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ARROW Clinical Data Analysis System:
An Integration of Statistical Analysis and Reporting

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ABSTRACT

The ARROW system, built with SAS® software, is a validated set of statistical analysis and reporting subsystems for clinical data. Originally developed in 1994, ARROW has been successfully applied to clinical data to generate clinical study reports and integrated summaries of safety and efficacy. The system has been enhanced over time to meet changing health authority and user requirements as well as new versions of the SAS system. ARROW is currently the standard statistical analysis and regulatory reporting system at Johnson and Johnson Pharmaceutical Research and Development, LLC. This paper introduces the ARROW system from the viewpoint of system design. It will discuss system scope, types of data analyses, modular structure, version control, diagnostics, archival and recovery. The major subsystems will be presented.

INTRODUCTION

Pharmaceutical companies have been challenged to streamline the generation of clinical study reports and integrated summaries in order to submit applications to health authorities and ultimately make medicines available to patients. Johnson and Johnson Pharmaceutical Research and Development, LLC has developed standardized global processes and systems to meet the challenges. The standard system, ARROW, includes multiple subsystems that process the raw clinical data in different formats to analysis datasets, perform analyses, and generate various outputs including listings, tabulations, and graphics. ARROW includes subsystems to generate electronic submission files compliant with FDA guidance and ICH specifications.

SYSTEM SCOPE

The ARROW system encompasses the entire process from raw clinical data to final regulatory outputs. It is applied to early development clinical trials (first in human, proof of concept, etc.), late development clinical trials (phase 1 to 3), medical affairs trials (phase 4 trials of marketed drugs), and integrated summaries. The system is flexible to meet the guidelines from global health authorities including FDA (US), MHRA and EMEA (Europe), and KIKO (Japan).

The ARROW system has been applied to the following clinical study designs.

- Parallel
- Cross-over
- Sequential

The major steps involved in processing clinical data follow.

1. Create analysis data
    - Read raw data, derive analysis variables, reformulate to analysis datasets including any transposes from horizontal to vertical structure.
2. Implement data analysis and statistical testing
    - Categorical
    - Continuous
    - Survival
3. Present analysis results
    - Tabulations
        - ASCII (i.e. SAS .LST), RTF, PDF
    - Graphics

        - EPS, PDF
    4. Generate report with hyperlinks
        - PDF

DESIGN CRITERIA

ARROW was designed with the following general requirements:

- Accuracy
    - The outputs are correct based on the inputs.
- Efficiency
    - The outputs are maximized based on programming effort.
- Reliability
    - Outputs can be dependably generated as needed.
- Reproducibility
    - Consistent outputs can be generated over time, given the same inputs and user selections.
- User Friendliness
    - The programmer has an intuitive interface with the system and can easily modify selections.

MODULAR STRUCTURE

Multiple subsystems comprise the ARROW system. As new requirements emerge, additional subsystems are developed with a consistent modular structure. Each subsystem contains the following modules.

1. Data preparation
2. Analysis
3. Display

The programmers are provided with sample “run panels”. Run panels are programs that call modules to perform functions. User guides, as well as documentation as comments in SAS programs, assist the programmer in selection criteria to generate specified outputs. Sample run panels for subject summary tables, i.e. adverse event incidence tabulations, would typically contain the following.

```
/* Initialize system and assign trial directories */
%fsetup61 (       trialnum = project name - trial name)

/* Data preparation */
%&ssprep_v (      inds = dtanal.adae,
                  outds = ssprep )

/* Data analysis */
%&ssanla_v (      inds=ssprep,
                  diststat=ssanla )

/* Display */
%&ssdspa_v (      diststat=ssanla,
                  outfile= rtf )
```

UNIFIED PROGRAMMING STYLE

The simplified code above illustrates key features of the ARROW system. There is central management of SAS

macros, program templates, and reference materials. ARROW utilizes a SAS autocall macro library containing programs performing specific functions. The call to the *FSETUP61* macro above initializes the ARROW system version 6.1, which is the current system running under SAS version 9.1.3. All clinical data are stored in a standard folder structure with standard names. In the *FSETUP61* program, the parameter *trialnum* specifies the project and trial locations, separated by a hyphen. The system assigns references to standard trial folders containing the raw and analysis data for the trial as well as trial specific program locations.

The sample code for adverse event incidence tables uses the ARROW Subject Summary (SS) subsystem performing categorical data analysis. The user interfaces minimize keyword parameters. Variable names are not hard coded in the system to allow for different and changing data standards. For example, the unique subject identifier variable is a parameter, with the default value *USUBJID*, a CDISC standard. If the input data followed other standards, the programmer would override the default by specifying the parameter in the call to the SAS macro.

Note the program flow above. The input adverse event dataset in the data preparation module is the permanent SAS dataset DTANAL.ADAE. The output dataset is temporary SAS dataset SSPREP, which is the input dataset in the analysis module, and the analysis output is stored in dataset SSANLA. Then the display module uses the information in the SSANLA dataset to output a rich text format (RTF) file. The RTF file is used directly by medical writers in reports, avoiding typing of adverse event incidence or other statistics. SAS .LST files are also available as output files.

VERSION CONTROL

The ARROW system contains validated programs that perform specific tasks. Global users request updates to accommodate new requirements through a change control process. Changes are evaluated by developers, and tested in a pre-production environment, before being released to production. There may be multiple versions of a program for the user to run. At initialization, the ARROW system defines the version of each program to use in the setup module.

We can see version control in the run panel above. The call *%fsetup61* instructs the system to initialize defaults for ARROW version 6.1, including use of SAS version 9.1.3. The call %&ssprep_v requires more explanation. There are multiple versions of the SS subsystem preparation module. We could call *%SSPREP61*, for example. *&SSPREP_V* is a SAS macro variable defined at initialization. Instead of hard coding version SSPREP61, The macro variable SSPREP_V is used to resolve the version. This adds flexibility, as a new version, e.g. SSPREP62, may be implemented. The same version control applies to analysis and display modules.

The ARROW version control facility allows so-called multi-version co-existence, i.e., multiple versions of ARROW system exist simultaneously under the same computer environment; such a feature is essentially needed for handling legacy studies in clinical trials.

USER INTERVENTION

In cases where the ARROW modules or system macros/defaults do not meet specific requirements for analysis or reporting, and change requests are not feasible, the programmer may copy an ARROW program to the local directory, modify it, and implement a process known as user intervention. User interventions add flexibility to ARROW and should be used only as a last resort when the requirements are clearly not standard and a new version of the ARROW program is inappropriate.

The ARROW function program *FINTER* is used to implement user intervention. The macro call, with required parameters, follows.

```
%&finter_v (    dir = ,
                module = ,
                version = );
```

DIR
SAS file reference to the folder containing the user-modified program.

MODULE
The program name

VERSION
Version of the program; the convention is to prefix a number with the letter “u” for user intervention.

If we needed to modify the SSPREP module, we would copy the program to the local directory, rename the program to SSPREPU1 and call the user intervention program as follows. Note that PGANAL is a standard folder under trials containing analysis programs.

```
%&finter_v (    dir = pganal,
                module = ssprep,
                version = u1);
```

SELF-DIAGNOSIS

In addition to the SAS notes, warnings, and other messages, the ARROW system displays three types of messages in the SAS log.

1. ARROW system message
    - Messages provide execution information including which modules are in process.
2. ARROW system warning
    - Warnings to make the user aware of issues, but not serious enough to stop program execution.
3. ARROW system interruption
    - Notifications of serious problems, causing the system to stop executing.

The messages enhance the value of the SAS log as a programmer debugging tool.

MAJOR SUB-SYSTEMS

The ARROW subsystems perform various clinical data tasks. The major subsystems are briefly described here.

Analysis Data Creation System (AD)

The AD system reads raw data and generates standard analysis datasets, which are the input datasets for analysis and reporting subsystems. The standardized structure of the analysis datasets enables pooling of clinical trials for integrated summaries. The system includes modules that generate the following key datasets.

- Subject Level (ADSL)
    - Contains demographic and baseline disease characteristics
    - Includes population variables (intent-to-treat (ITT), safety, per-protocol, etc.)
    - One record per subject
- Exposure (ADEX)
    - Contains detailed trial medication information
    - Includes total daily dose, dates, and durations
- Exposure Summary (ADES)
    - Contains summarized subject trial medication information

Information from the ADSL and ADEX datasets are joined with other raw datasets to generate additional analysis datasets. The trial medication dates and doses in ADEX are used to assign relative days and onset dose in other analysis datasets including the following.

- Medical History (ADMH)
- Concomitant Medications (ADCM)
- Disposition (ADDS)
- Physical Examination (ADPE)
- Adverse Events (ADAE)
- ECG (ADEG)

- Laboratory tests (ADLB)
- Vital signs (ADVS)
- Others (ADxx)

Demographic Analysis System (DM)

The demographic system is used to summarize demographic data, and display descriptive statistics as well as between group comparisons (p-values).

Descriptive statistics options:

- Continuous data (e.g. age)
  - number of values assessed (N)
  - mean and /or confidence interval with different significance levels
  - standard deviation (SD)
  - median and/or confidence interval with different significance levels
  - range
- Categorical data (e.g., gender, race)
  - number of values assessed (N)
  - distribution (frequency table)

Statistical test options:

- Chi-square test
- Fisher's exact test
- Cochran-Mantel-Haenszel Test
  - row mean scores differ
  - general association
  - non-zero correlation
- Kruskal-Wallis test
- Wilcoxon rank sum test
- Van Elteren test
- ANOVA without interaction
- ANOVA with interaction

Actually, the DM sub-system is a combined statistical analysis tool for both continuous and discrete data without nesting. It can be applied for different purposes, such as dose administration, vital signs, risk management or exposure summary, … and so on.

Subject Summary System (SS)

The Subject Summary system is a general tool used to summarize and display categorical data. This system is applied to adverse events, concomitant medications, medical history, physical examination, protocol deviations, and other clinical datasets where results are presented as counts and percentages in categories.

The following statistical comparisons are available.

- Within-group comparison
- Between-group overall comparison
- Between-group pairwise comparison

Statistical test options:

- Chi-square test
- Fisher's exact test
- Confidence interval for binomial proportion
- Odds-ratio
- Cochran-Mantel-Haenszel Test
  - row mean scores differ

    - general association
    - nonzero correlation
- Van Elteren test

Adverse Events Analysis System (AE)

Adverse event data are analyzed using the Subject Summary system. The AE system contains macro calls to the SS system that generate the following standard tables.

- Incidence of Adverse Events by Body system, Preferred Term and Included Term
- Incidence of Adverse Events by Body system, Preferred Term
- Incidence of Adverse Events by Preferred Term
- Incidence of Adverse Events by Severity
- Incidence of Adverse Events by Relation to Medication
- Incidence of Adverse Events by Action Taken
- Incidence of Adverse Events by Subject Outcome
- Incidence of Adverse Events by Severity and Relation to Trial Medication
- Incidence of Adverse Events by Toxicity
- Incidence of All Adverse Events by selected sub-group (gender, race, etc.)

Efficacy Analysis System (EF)

The Efficacy Analysis System is used to analyze discreet, ordinal, and continuous clinical data. Results can be displayed as graphics, standard SAS files(.LST), and as Rich Text Files that are imported directly into clinical study reports.

- Statistical test options:
- Chi-square test
- Fisher's exact test
- Cochran-Mantel-Haenszel Test
    - row mean scores differ
    - general association
    - nonzero correlation
- Friedman Test
- Bonferroni Adjusted Friedman Test
- Kruskal-Wallis Test
- Van Elteren Test
- Cochran-Amitage Test
- Breslow-Day Test
- Page Test
- Jonchkerre-Terpstra Test
- One-way ANOVA
- Multiple-way ANOVA without interaction
- Multiple-way ANOVA with interaction
- Multiple-way ANCOVA without interaction
- Multiple-way ANCOVA with interaction
- Some GLM models with selected class variables and factors
- MIXED models with both fixed and random effects
- Fisher LSD Test for pairwise comparison
- Donnett Test for multiple comparisons
- Dunn Test for multiple comparisons
- Exact Wilcoxon Ranksum Test
- Logistic Regression
- Survival Data Analysis

Laboratory Analysis System (LB)

The Laboratory system analyzes and reports clinical laboratory (hematology, blood chemistry, urinalysis, and immunology) data. The system is an application of the efficacy analysis system. The Laboratory Analysis System includes the following standard tables and listings.

- Mean Change From Baseline To End Point
- Change From Baseline Over Time
    - Simple or detailed report selections
- Shifts in Laboratory Values (i.e. within reference range at baseline to above or below reference range post treatment)

Report Listing System (RL)

The Report Listing system is used to produce clinical data listings. Various output options are available to display the data and automatically align report columns, wrap long text values, paginate, etc. The files may be output as standard SAS text files (LST) or rich text format (RTF).

Narrative Listing System (NR)

The Narrative Listing system is used to produce subject profiles for health authority, e.g. FDA, submission. Subject profiles are displays of study data of various modalities collected for an individual subject and organized by time. The NR system implements the report listing system to generate subject listings of demographics, adverse events, exposure, and other clinical domains. The listings are reformatted to include key patient information in report headers and sort all domains by patient. The files are split into individual files by patient in order to produce indexed PDF files for health authority submission.

In general, health authorities require subject profiles for clinical trial subjects that died, had a serious adverse event, discontinued due to an adverse event, or had an adverse event of interest (as specified). The NR system has the flexibility to accommodate changing criteria based on the drug studied and health authority needs.

Statistical Graphic System (GR)

The ARROW Statistical Graphic System is used to produce different types of graphical displays, including mean plots, vertical bar charts, horizontal bar charts, box plots, line plots, dot plots, and survival curves. The graphic system consists of graphic modules that accept data from data preparation or analysis modules of other ARROW subsystems. This architecture guarantees the consistency between the ARROW tabulation and graphic displays. It reflects of the nature of the entire ARROW system. Around the analysis kernel, tabulations and graphics are two approaches for presenting the same results.

Categories of graphic programs:

- General graphic modules
    - generate graphs with input from data preparation modules.
- Efficacy graphic modules
    - generate graphs with input from analysis modules
- Supporting graphic macros
    - arrange annotation, page headers, orientation, axes, and other graph formatting

General graphic modules generate the following graphics.

- Mean SD/SE plots
- Vertical bar charts
- Horizontal bar charts
- Box plots
- X-y curves
- Dot-type plots, including scatter, regression and needle plots

Efficacy graphic modules generate the following graphics.

- Least square mean plots

- Vertical bar plots with confidence intervals
- Survival plots
- Plots of point estimation and confidence intervals

Graphical Subject Profile System (GS)

The Graphical Subject Profile System produces visual displays of the relationships of data over time. The system offers different visualizations to display baseline characteristics, treatment and effect.

- Text elements (not time related) e.g. demographic characteristics
- Single events, e.g. drug administration
- Episodes with duration, e.g. adverse events
- Continuous variables in time, e.g. laboratory values
- Reference points, e.g. start of treatment

The data visualizations generated by the graphical subject profile system are used on an ongoing basis during clinical trials to assess safety as a medical safety review tool.

Risk Management Analysis System (RM)

The European Medicines Agency (EMEA) routinely requires a risk management plan (RMP) as part of the medicine approval process in Europe. The US Food and Drug Administration (FDA) may require a risk evaluation and mitigation strategy (REMS) to ensure the benefits of a drug outweigh the risks. The Risk Management Analysis System was incorporated into ARROW to meet new and changing health authority requirements for risk information.

The RM system generates the following report types.

- Exposure summaries
    - Generated by the DM system
- Adverse event summaries
    - Generated by the SS system
    - Includes pairwise comparisons of active doses to placebo
        - Odds ratio and confidence intervals reported

Electronic Submission System (ARROWPDF)

The electronic submission system (ARROWPDF) is used to generate data and documentation conforming to FDA guidance and ICH specifications. The system requirements follow.

- Individual Version 5 SAS transport files (.xpt) for each clinical domain
- Data definition tables (define.pdf and/or define.xml), which describe the datasets for each study, specific data analysis (e.g., population PK), and integrated summaries
- Annotated case report forms (blankcrf.pdf)
- The entire submission includes a directory structure with navigational tools (hyperlinks).

The ARROWPDF modules perform these tasks.

- Optional module to prepare pharmacokinetic data and metadata.
- Required exception report checks the dataset contents for compliance with specifications, including file names, dataset and variable labels, etc.
- Optional module to check transport file sizes and divide files based on health authority requirements
    - Current FDA guidelines require confirming with review division for files greater than 100 MB. There is no size limit for CDISC SDTM files.
- Required module to generate individual SAS transport files.
- Required module to generate dataset and variable metadata (labels, comments, derivations, etc.)
- Required module to generate the data definition table with hyperlinks.

RECOVERY PROCESS

The recovery process was developed to ensure reproducibility of ARROW outputs over time. There are ongoing change requests, minor and major system updates, so it is important to be able to reproduce results from legacy clinical studies. The ARROW modules used in the recovery process are contained in the ARROW Quality Control (QC) subsystem. The archived system directory contains previous versions of all programs.

When a legacy output is identified for reproduction, the programmer identifies the original program that generated the output. The program is rerun using current ARROW modules. The QC system has tools that compare files and list differences in SAS output (.LST) and RTF files. If differences are found, the programmer uses another QC tool that searches the archived system for the latest versions of the modules that were in production on the date of the original output file. These tools automate the reproducibility of legacy outputs.

CONCLUSION

The ARROW system has been adapted over time to meet changing requirements from internal users and global health authorities. The modular structure and unified programming style allow for continuous enhancement in a validated environment. Statistical programmer effectiveness is optimized when tools are available to handle complex requests. The subsystems within ARROW have proven valuable tools for clinical data analysis and reporting in a changing regulated environment.

REFERENCES

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http://www.cdisc.org/standards/index.html

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