PharmaSUG China 2019 - Paper DM-015

Ease of Use by Clinical Trial Data: Analysis in an End- To -End Clinical Data Management to Submission Process

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ABSTRACT

Pharmaceutical companies continue to focus on improving the clinical trial analytics process capacity. Refer to this requirement, we expect an integrated environment that contains data management, metadata management and analytics around the clinical trials. In addition, companies are looking to have this information aggregated across trials, so they can analysis and evaluate the information to improve future clinical trials. Regarding these challenges, design, implement and analysis the complex clinical trials to tackle life threatening diseases faced with continuous pressure.

INTRODUCTION

To resolve the challenges, to make our clinical trial data more easy to use and our clinical data management process more effective, we create a demo here that setup three goals to implement a use case of Nicardipine Study (Figure 2). In clinical data management and analysis part, we provide a single information management system integrates with SAS programing environment and metadata management study which compliance with CDISC standard; In clinical data analysis report part, we provide automated reporting tools as aspect of different trail design purpose to generate clinical statistical report across all domain tables in the study; In finally submission part, we provide button click to validate and generate Define-XML automatically.

- **Goal 1- Clinical Data Management**
  To enable all sites working together in the same framework to manage your clinical data, metadata; perform analysis and trail design by SAS® LSAF.
- **Goal 2- Clinical Data Analysis**
  To perform clinical data analysis to get valuable reports in a matter of seconds automatically, enable all key participants in the trial process to explore trends and outliers to share valuable results by SAS® JMP Clinical.
- **Goal 3- Submission to Define-XML**
  To validates and generates Define-XML of transmitting metadata that describes any tabular dataset structure automatically to accelerate regulatory approval process by SAS® LSAF.

With the three goals above, let's see how SAS uncover the optimal capabilities of data analysis in an end- to -end clinical management to submission process. (Figure1)

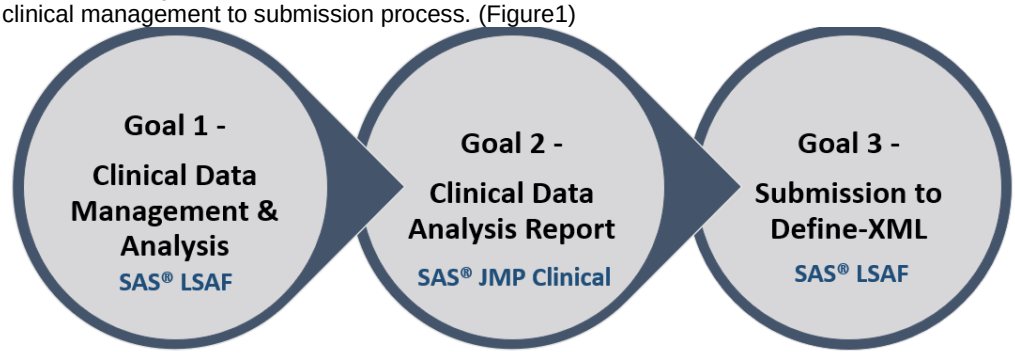


Figure 1. Goals overview

Nicardipine Study

Study of the effects of Nicardipine on patients suffering from recent aneurismal subarachnoid hemorrhages (Clarke, et al. 1993a, 1993b). 906 patients were included in this randomized double-blind placebo-controlled study; 449 patients received nicardipine while 457 received the placebo. Patients in each group were balanced with regard to prognostic factors for overall outcome. Nicardipine and the placebo were delivered continuously at 0.15 mg/Kg/hr for up to 14 days and patients were followed for up to 120 days following administration of the drugs.

Figure2. Use case background

GOAL 1- CLINICAL DATA MANAGEMENT & ANALYSIS

Data management is essential to overall clinical trial, as its key deliverable is the data to support submission. Assuring the overall accuracy and integrity of the clinical trial data is the core business in the data management. Also, clinical data management is involved in all aspects of processing the clinical data, working with a range of computer applications, database systems to support collection, standardization and management of subject or trail data. And there are different key members involved in data management and analysis process which would be Project Manager, Data Manger, Database Administrator, Database Programmer, Developer, Clinical Data Associate, SAS Programmer, Statistician and so on. So, questions come out:

1. Can all partners and data work at the same stage?
2. Can we centralize and standardize clinical data in the Study?
3. How to do deeper investigation in current data?

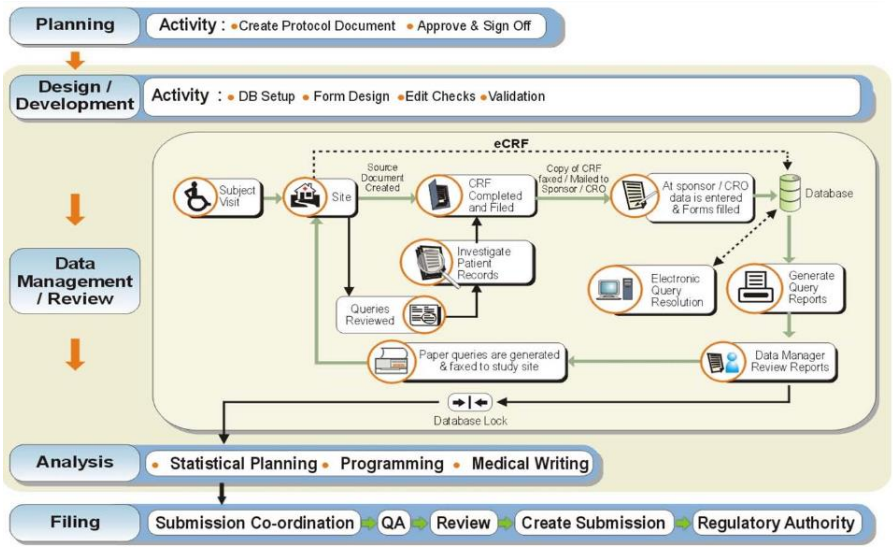


Figure 3. Clinical Trail Process

1. ALL PARTNERS AND DATA WORK AT THE SAME STAGE

To enable clinical data management in Nicardipine Study of all sites and all the key stakeholders working together, SAS® LSAF (Appendix: SAS® LSAF Introduction) consolidates your clinical information into a single global repository. In the Repository of SAS® LSAF, you can customize any clear and robust hierarchies to satisfy the business needs in your organization. (Figure 4)

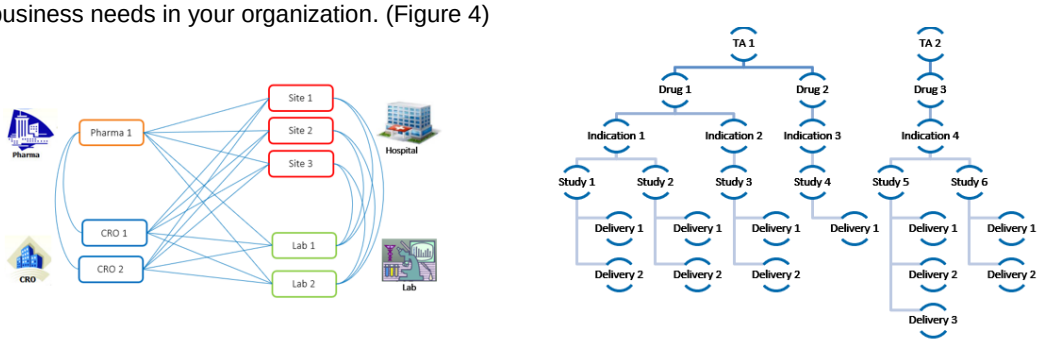
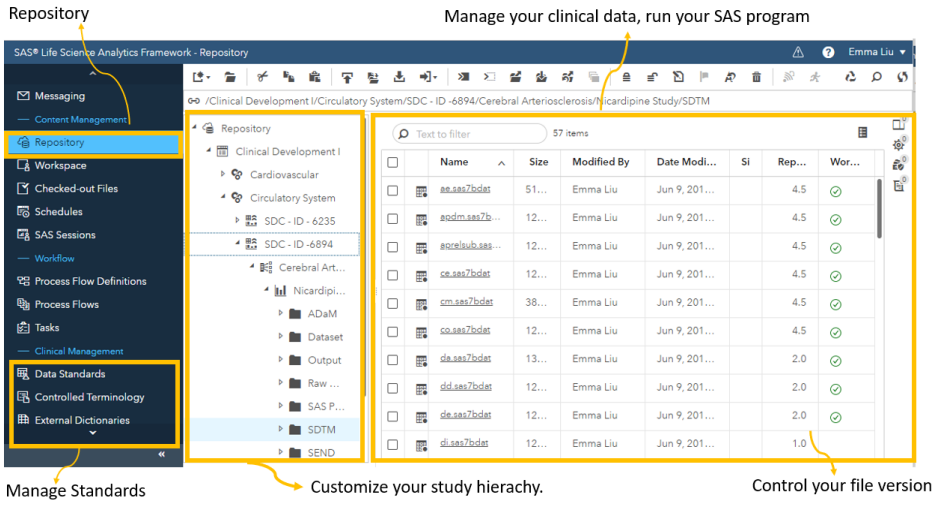


Figure 4. Hierarchy against site distribution

In the Repository of SAS® LSAF, you can manage your raw data, clinical data, metadata, reports and SAS programs which is just like a centralized information manage system. Different roles across the globe can gain a single version of the truth. With global access to a clinical analytics foundation for all authorized development team members, regardless of organization, they'll no longer waste time and resources working on different systems across multiple geographies and organizations. (Display 1)



Display 1. Build up Nicardipine Study hierarchy in Repository

2. CENTRALIZE AND STANDARDIZE CLINICAL DATA IN THE STUDY

As above, we are now working together. The coming faced question is: How can we easily manage and generate the output comply the requirement of CDISC standards? SAS® LSAF supports prebuilt CDISC Standards of tabulation and analysis as global standard (Figure 5. Global Standard). Base on the global standard, we can setup specific trial design. As in our Nicardipine Study, it does not use all of the available variables in all of the available tables from global standard, it may use a specific subset of global Standards. With that said, the metadata in the study has to be pared down to match what was actually needed in the Nicardipine Study's trail design, and it's continuously being updated during analysis process. SAS® LSAF supports Study metadata structure (Figure 5. Independent Study) which is completely compliance with CDISC Define-XML structure (Figure 5. Submission Define-XML). We will demonstrate three parts to implement metadata of Nicardipine Study:

- Refine Domain, Column and Codelist Metadata
- Design Value Level Metadata
- Design Analysis Results Metadata

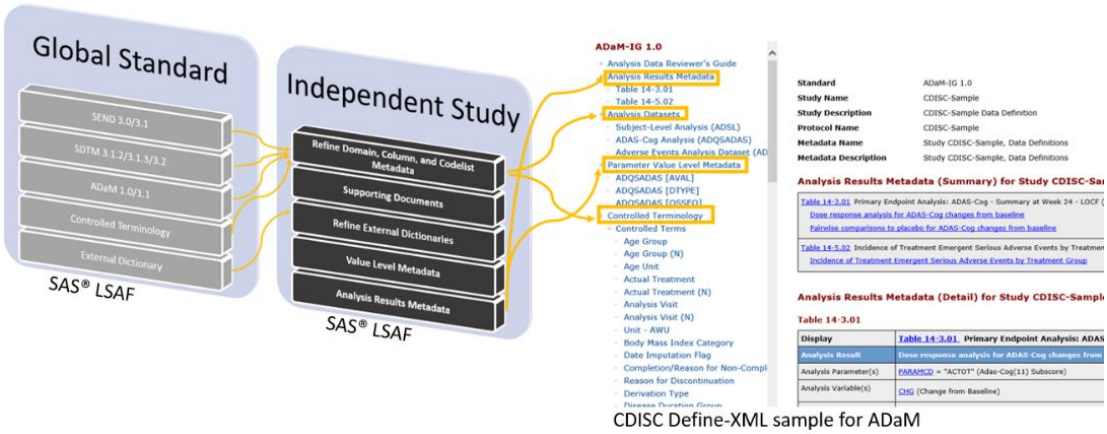
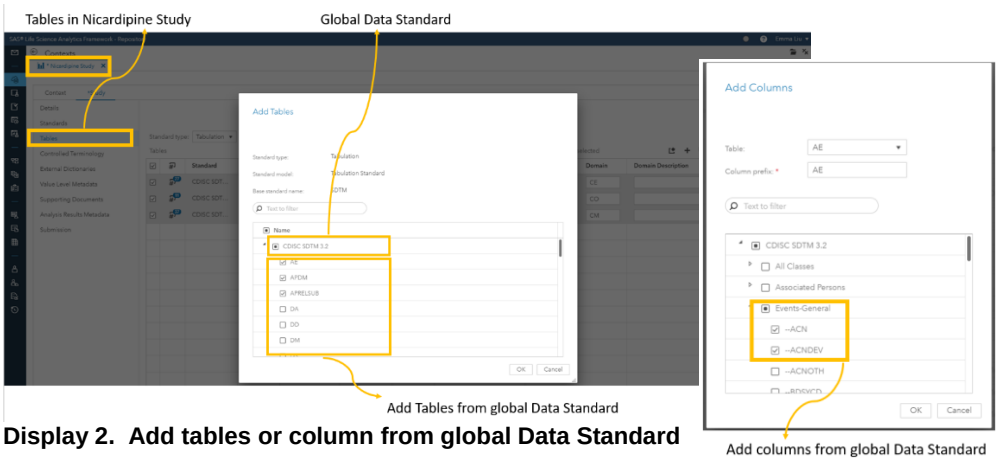


Figure 5. Global Standard VS. Independent Study VS. Submission Define-XML

Refine Domain, Column and Codelist Metadata

In the Nicardipine Study, we can directly pick the metadata tables or columns from global Standards that is relevant to our investigating study. This includes shrinking down to only the tables, variables or controlled terminology you want to be added to the study from global Standard. (Display 2)

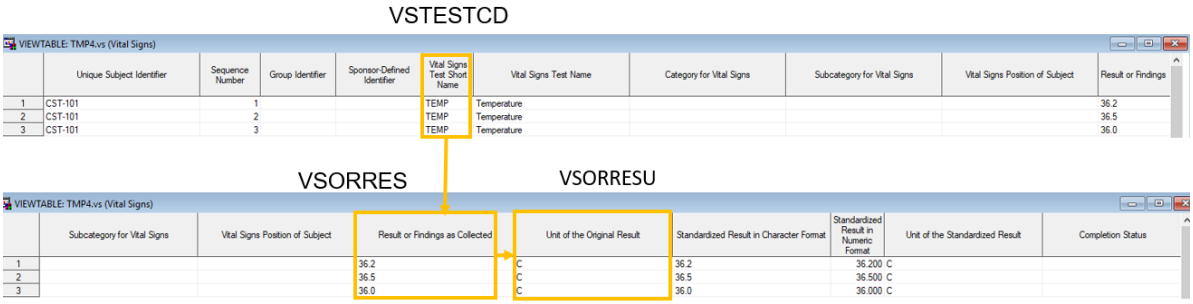


Display 2. Add tables or column from global Data Standard

Design Value Level Metadata

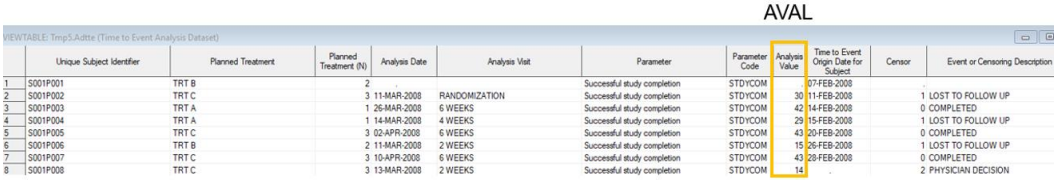
In some cases, to provide sufficient details of data review and analysis, we need to design VLM (Value Level Metadata) which enables the specification of the metadata of a variable under conditions involving one or more other dataset variables. SAS® LSAF can maintain VLM easily like examples below:

In the Nicardipine Study, SDTM VS domain table, we have two Variables: VSORRES and VSORRESU. They are expected to be described with value-level metadata because their data is made up of multiple data. The set of values of VSORRES (Result or Findings as Collected) and VSORRESU (Unit of the Original Result) for different values of VSTESTCD (Vital Signs Test Short Name), define unique data elements. Each data element will have at least one distinctive attribute. For instance, the value set for VSORRESU (Result or Findings as Collected) for VSTESTCD= ”TEMP” (Temperature) will differ from the value set of units for VSORRESU =”C”(Celsius) as different Celsius of temperature. (Display 3.)



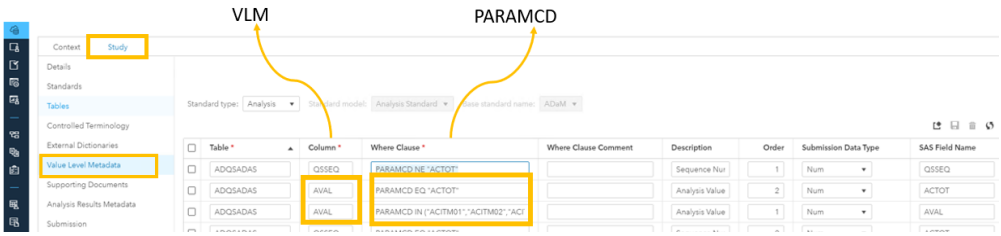
Display 3. VLM in VS Domain Table

Another example in our Nicardipine Study, ADaM ADTTE table, the metadata for variable AVAL for tabular data that uses that variable and follows the ADaM model may include different Source information for different subsets of the PARAMCD values. It also represents as VLM. (Display 4)



Display 4. VLM of AVAL in ADTTE Table

From SAS® LSAF Study-> Value Level Metadata, you can directly define the VLM “AVAL” by cell-based editing with PARAMCD to identify metadata using any operators supported by SAS, such as NE, EQ, IN () per your protocol. (Display 5)



Display 5. VLM in the Study

Design Analysis Results Metadata

As we know, ARM (Analysis Result Metadata) as part of CDISC Define-XML provides traceability from results in statistical Display to the data in the analysis datasets. It is proposed by CDISC to analysis the primary and secondary endpoints of your trail design. ARM's straightforward solution would be to take the metadata proposed by CDISC and enter it manually for each table or figure that is part of the analysis of primary and secondary endpoints.

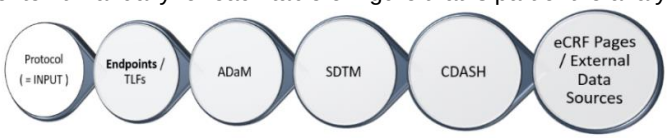
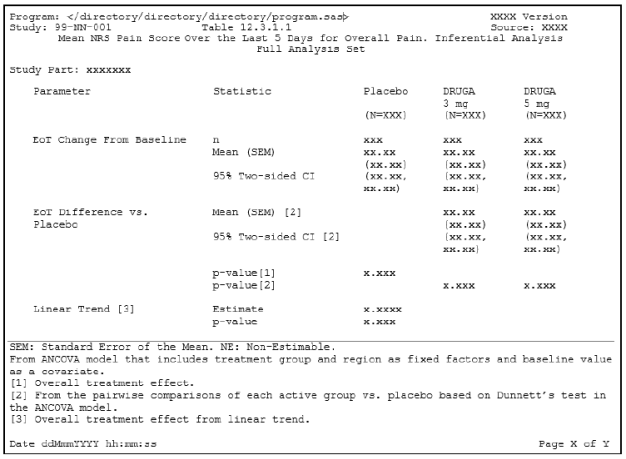


Figure 6. Traceability of ARM

Let's see the ARM example in our use case. It focuses on traceability from results in statistical Display to the data in the analysis datasets. Also, SAS LSAF can help us easily to create it.

Based on the analysis Display (Figure 7), information in ADaM metadata, Statistical Analysis Plan (SAP), Tables Listings and Figures (TLF) specifications, and TLF metadata, the ARM was created which compliance with Version 2.0 of the CDISC Define-XML. (Table 1)



```
Program: </directory/directory/directory/program.sas>                    XXXX Version
Study: 99-NN-001          Table 12.3.1.1                                 Source: XXXX
       Mean NRS Pain Score Over the Last 5 Days for Overall Pain. Inferential Analysis
                                Full Analysis Set

Study Part: xxxxxxx

    Parameter                Statistic            Placebo      DRUGA        DRUGA
                                                                3 mg         5 mg
                                                  (N=XXX)      (N=XXX)      (N=XXX)

    EoT Change From Baseline n                    xxx          xxx          xxx
                             Mean (SEM)           xx.xx        xx.xx        xx.xx
                                                  (xx.xx)      (xx.xx)      (xx.xx)
                             95% Two-sided CI     (xx.xx,      (xx.xx,      (xx.xx,
                                                  xx.xx)       xx.xx)       xx.xx)

    EoT Difference vs.       Mean (SEM) [2]                    xx.xx        xx.xx
    Placebo                                                    (xx.xx)      (xx.xx)
                             95% Two-sided CI [2]              (xx.xx,      (xx.xx,
                                                               xx.xx)       xx.xx)

                             p-value[1]           x.xxx
                             p-value[2]                        x.xxx        x.xxx

    Linear Trend [3]         Estimate             x.xxxx
                             p-value              x.xxx

SEM: Standard Error of the Mean. NE: Non-Estimable.
From ANCOVA model that includes treatment group and region as fixed factors and baseline value
as a covariate.
[1] Overall treatment effect.
[2] From the pairwise comparisons of each active group vs. placebo based on Dunnett's test in
the ANCOVA model.
[3] Overall treatment effect from linear trend.

Date ddMmmYYYY hh:mm:ss                                                  Page X of Y
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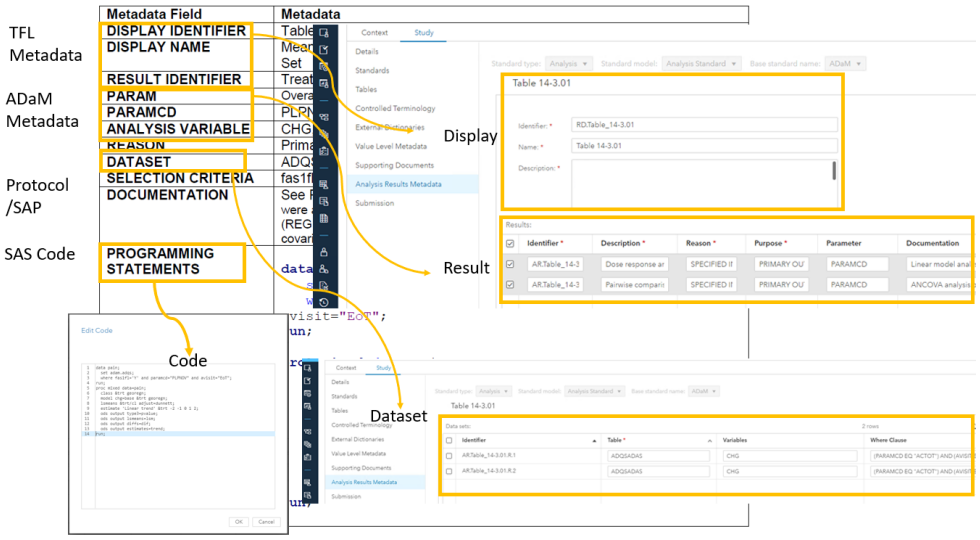
Metadata Field	Metadata
DISPLAY IDENTIFIER	Table 12.3.1.1
DISPLAY NAME	Mean NRS Pain Score Over the Last 5 Days for Overall Pain. Full Analysis Set
RESULT IDENTIFIER	Treatment difference results (Mean, confidence interval, p-value)
PARAM	Overall Pain Score during the 5-day Period
PARAMCD	PLPNOV
ANALYSIS VARIABLE	CHG, BASE, TRT02AN, GEOREGN
REASON	Primary efficacy analysis as pre-specified in protocol
DATASET	ADQS
SELECTION CRITERIA	fas1fl='Y', paramcd='PLPNOV', trt01pn~=., avisit='EoT'
DOCUMENTATION	See Protocol Section XX for details. Program: program_ex1.sas. NRS scores were analysed using an ANCOVA model which included dose group and region (REG1 and REG2) as fixed factors and baseline NRS pain score of overall pain as a covariate.

PROGRAMMING STATEMENTS	`data pain;`
	`  set adam.adqs;`
	`  where fas1fl='Y' and paramcd="PLPNOV" and avisit="EoT";`
	`run;`
	
	`proc mixed data=pain;`
	`  class &trt georegn;`
	`  model chg=base &trt georegn;`
	`  lsmeans &trt/cl adjust=dunnett;`
	`  estimate 'Linear trend' &trt -2 -1 0 1 2;`
	`  ods output type3=pvalue;`
	`  ods output lsmeans=lsm;`
	`  ods output diffs=dif;`
	`  ods output estimates=trend;`
	`run;`

Figure 7. Analysis Statistical Display

Table 1. Analysis Results Metadata

As we talked above, the information needed for the ARM does not come from one place only. It comes from the SAP, TLF specifications, from ADaM metadata, and even from SAS programs. To make these various of clinical data being centralized and standardized in one place, we implement ARM to SAS® LSAF Study. The ARM in the Study of SAS® LSAF totally compliance with Version 2.0 of the CDISC Define-XML structure. You can directly define the ARM by cell-based editing with the same structure as Table1. Otherwise, these works need be done in many tools and traverse across trails which waste a lot of time. With the ARM of Study provided by SAS®LSAF, we minimize the work for the standard values, we enable you focus on new or unexpected values for deep analysis. (Display 6)

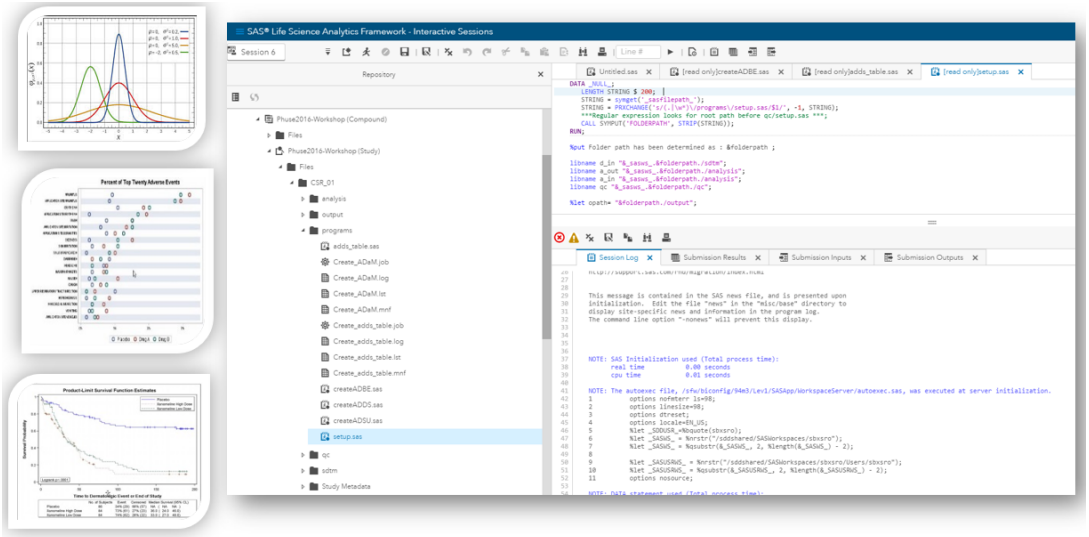


Display 6. Analysis Result Metadata in the Study of SAS® LSAF

3. DEEPER INVESTIGATION IN CURRENT DATA

Through a submission to the end, it may include many of ARM against different analysis Display results in your trial design. Any of the trail design can be designed in SAS® LSAF which inlcude some common clinical trial designs, such as: single-arm trials, placebo-controlled trials, crossover trials, factorial trials, noninferiority trials, and designs for validating a diagnostic device. Considering of this, we may design a great many of SAS programs to achieve clinical data analysis.

SAS® LSAF provides SAS coding environment to design, run, and debug your SAS program. In the Code Editor of SAS® LSAF, you can perform any of the coding related works with SAS. Batch of SAS programs can be converted as Job and Schedule Job which enables you easily to trace inputs and outputs files against analysis result, debug your code, and run your code as any time as you want. The outputs files of your analysis report can be generated to Repository with version control function for you easy to trace and debug the running results for all key participators. Also, the outputs files can be generated to Workspace which is your private workshop to debug and testing your code (Display 7).



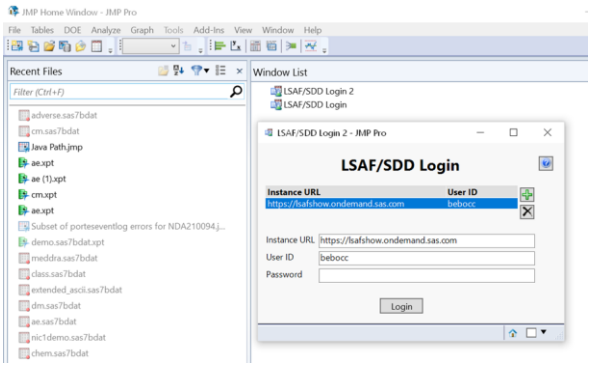
Display 7. SAS® LSAF Code Editor generated analysis report

GOAL 2- CLINICAL DATA ANALYSIS REPORT

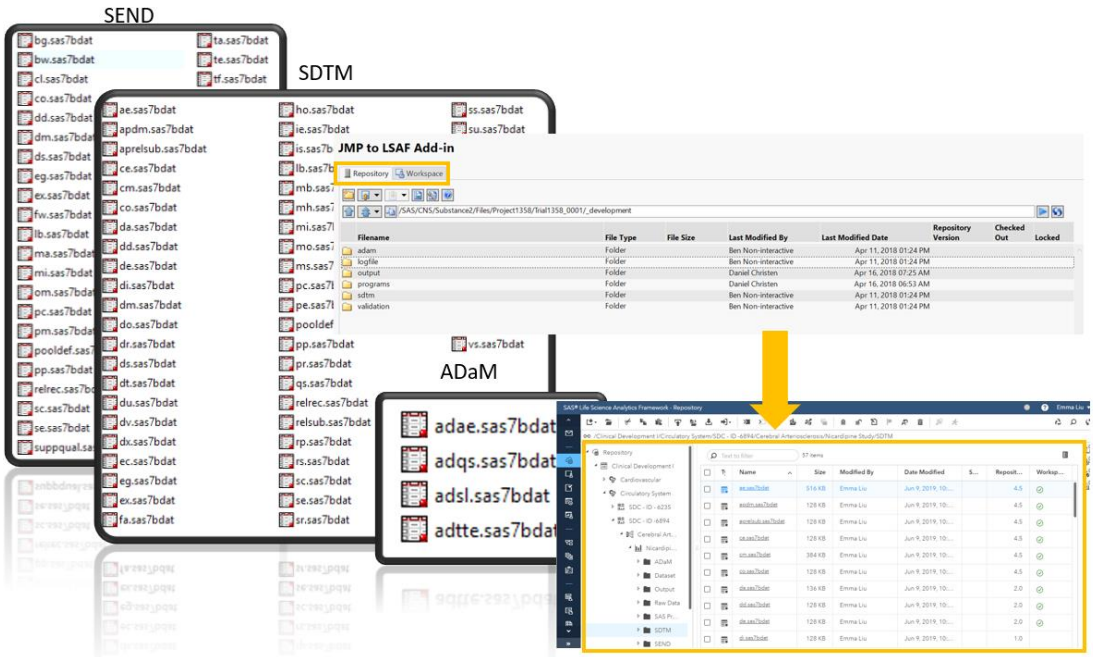
Furthermore, instead of design batch of SAS programs, if we can perform clinical data analysis to get valuable reports in a matter of seconds automatically, even though people with no SAS program skills can explore trends and outliers to share valuable results, that we would be gain more efficacy of our clinical analysis. JMP Clinical, a powerful software system for integrated statistical analysis of clinical data. JMP Clinical software consists of approximately 100 independent reports. It provides sophisticated analysis of safety review data collected during clinical trials of new drugs. Like all JMP products, JMP Clinical has data visualization capabilities and a user-friendly environment. This means that even though medical reviewers, many of whom are physicians with little training in statistics, can more easily discover patterns and hidden trends in data on adverse events, concomitant medications, lab results, patient profiles and so on.

JMP CLINICAL TO SAS® LSAF ADD-IN

From JMP Clinical, we can analysis the prepared clinical trial data from SAS® LSAF Nicardipine Study. JMP Clinical provides SAS® LSAF Add-In. User can directly configure SAS® LSAF Instance URL and User ID in JMP Clinicals (Display 8). With JMP Clinical to SAS® LSAF Add-in, statistician can directly access to SAS® LSAF Repository or Workspace which integrates with all the domain models of Interventions, Events, Findings, Trial Design, Special Purpose, Findings About and Special- Purpose Relationship which across SDTM, ADaM and SEND in Nicardipine Study to perform statistical analysis. (Display 9)



Display 8. SAS® JMP Clinical Add-In plus to SAS® LSAF



Display 9. JMP to LSAF Add-in Repository and Workspace

CLINICAL DATA ANALYSIS REPORTS

Due to limited space, in this section we only introduce one example of data analysis report against Findings Laboratory Test Result (LB) in JMP Clinical. For more information you can see Appendix for details.

Figure 8 shows JMP Clinical's capability in statistical analysis of Findings AVOVA in Laboratory Test Result (LB). It provides the comprehensive summary of ANOVA model fitting results via Volcano Plots, Dendrogram Cluster Head Map, Parallel Plot and Principal Components Plot. Even though people with no programming experience, they can run this report using default settings generates the tabbed report in Nicardipine Study of JMP Clinical.

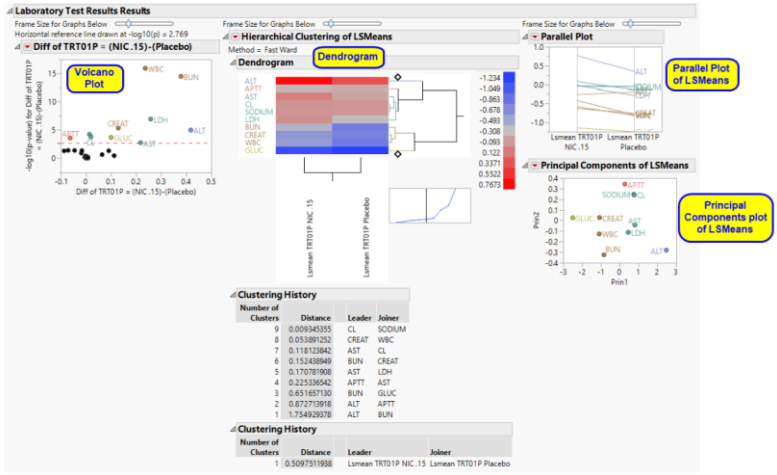


Figure 8. Laboratory Test Results

From this Volcano Plots (Figure 9), we can see a convenient way to summarize a specific hypothesis test across all Findings Laboratory tests. It is based on a single hypothesis of interest and each point in the plot is a Findings test (for example: ALT). The X axis represents a difference of lab result by subject being administrated of NIC .15(Nicardipine. dose) and Placebo in the planned treatment of period 01; The Y axis represents its corresponding -log10(p-value); The Volcano plots have a characteristic "V" shape, this is because estimates near zero (0) tend not to be significant, the significant are those away from zero tend to have smaller p-values and larger -log10(p-values). So that the significant Findings tests are those in the upper left and right quadrants of the plot (APTT and ALT), akin to exploding pieces of molten lava. The red dashed horizontal line represents a significant criterion computed by some multiple testing method. From the report, it's easy to tell the efficient screening of lab scores that differ between treatment groups.

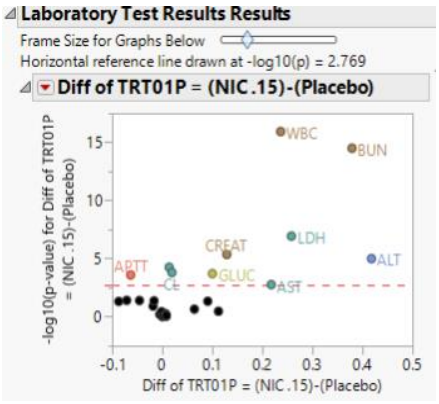


Figure 9. Volcano Plots

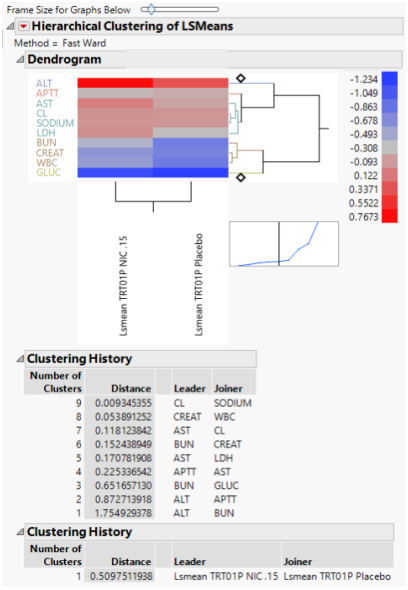


Figure 10. Dendrogram Cluster Heat Map

From Dendrogram Cluster Heat Map plot (Figure 10), we can compare expression patterns for all significant Findings tests simultaneously. The standardized least squares means (LSMeans) for every Findings test that is significant in at least one volcano plot are clustered both horizontally and vertically and depicted with the heat map. Each row of the heat map is a Findings test and each column is a distinct LS mean. From the report, statistician can observe which Findings tests and LS means have similar profiles. So that we can directly tell the LS means of NIC.15 and Placebo have similar profiles on Findings test of GLUC, ALT and APTT.

Later, we can use Parallel Plot (Figure 11) to show the unstandardized LS means which enable statistician to see degree of overall results for the same set of significant Findings tests.

Finally, we can use Principal Components plot (Figure 12) to provide an alternative way of comparing significant LS means. It computes a principal component analysis (SPC) on them and plots the first two components. This projects high-dimensional patterns into two dimensions (Prin1 and Prin2). Principal Components plot can help statistician easy to identify outliers. From the report, we can see that points near the outer virtual bounding ellipse are well-explained by the first two principal components. So Findings test of ALT well explained Prin1 and APTT well-explained of Prin2.

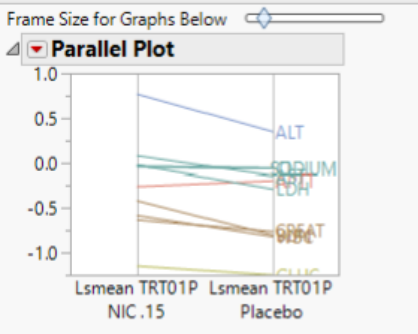


Figure 11. Parallel Plot

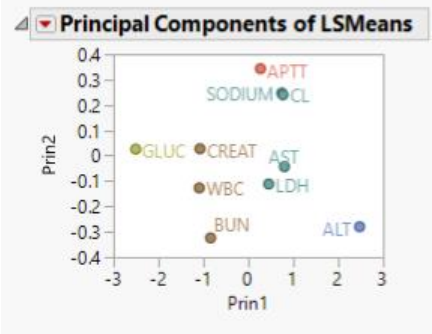


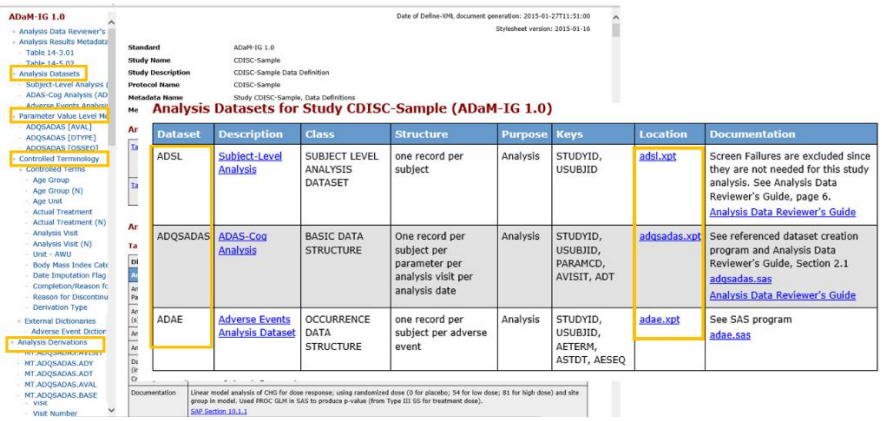
Figure 12. Principal Components plot

From goal 2, we see JMP Clinical extract the maximum amount of useful information from clinical data to reveal hidden data's value. So that we can get various of visualization capabilities report from JMP Clinical to perform clinical data analysis and back to SAS® LSAF to perform the later submission related activities in goal 3.

GOAL 3- SUBMISSION TO DEFINE-XML

CDISC DEFINE-XML

As we know, Define-XML transmits metadata that describes any tabular dataset structure, it is used to be certain that data submitted to the FDA adheres to CDISC. Define-XML can help the regulatory agencies quickly understand the data structure (Display 10). Let's see how to generate it easily.



Analysis Datasets for Study CDISC-Sample (ADaM-IG 1.0)

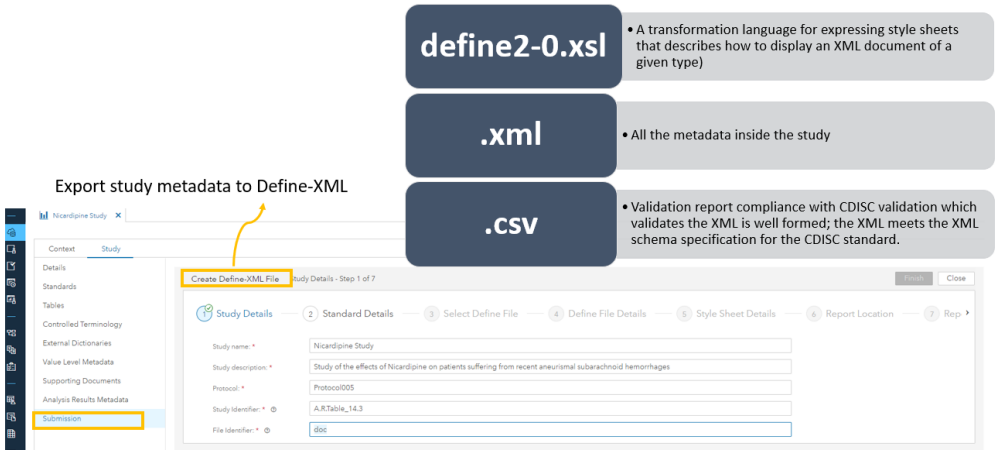
Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
ADSL	Subject-Level Analysis	SUBJECT LEVEL ANALYSIS DATASET	one record per subject	Analysis	STUDYID, USUBJID	adsl.xpt	Screen Failures are excluded since they are not needed for this study analysis. See Analysis Data Reviewer's Guide, page 6. Analysis Data Reviewer's Guide
ADQSADAS	ADAS-Cog Analysis	BASIC DATA STRUCTURE	One record per subject per parameter per analysis visit per analysis date	Analysis	STUDYID, USUBJID, PARAMCD, AVISIT, ADT	adqsadas.xpt	See referenced dataset creation program and Analysis Data Reviewer's Guide, Section 2.1 adqsadas.sas Analysis Data Reviewer's Guide
ADAE	Adverse Events Analysis Dataset	OCCURRENCE DATA STRUCTURE	one record per subject per adverse event	Analysis	STUDYID, USUBJID, AETERM, ASTDT, AESEQ	adae.xpt	See SAS program adae.sas

Display 10. CDISC Define-XML sample of ADaM

EXPORT/IMPORT DEFINE-XML IN THE STUDY OF SAS® LSAF

SAS® LSAF supports validates and generates the Submission to Define-XML v2.0(the most current version of CDISC's recommended version). With a friendly export wizard of button-click-by user interface, user can easily generate the whole Nicardipine Study's metadata as Define-XML. In the export wizard of SAS® LSAF, output files will be generated to Repository including Define-XML file, .XSL file which is the transformation language to express style

sheets of XML structure, and .csv file of validation report compliance with Define-XML standard (Display 11).



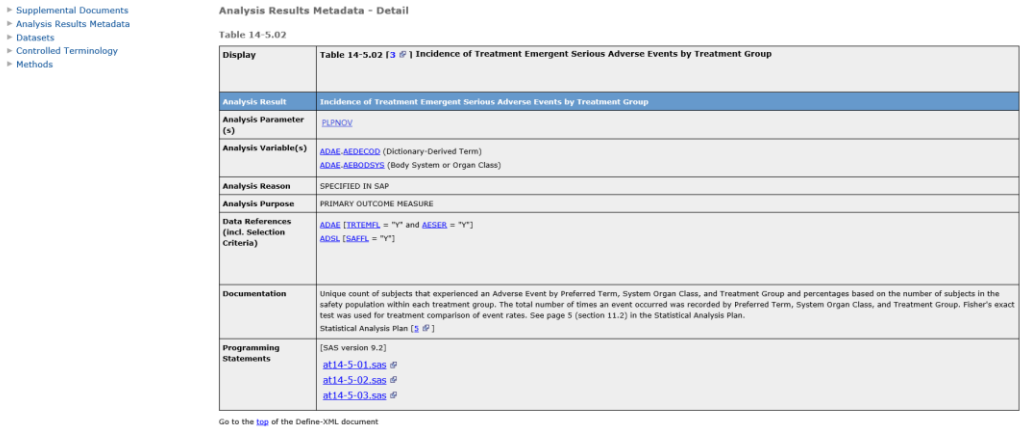
Display 11. Files generate from Study Submission

Furthermore, we also support importing Study metadata from Define-XML. That means, organization can perform information transformation to share, continue to manage data and analysis by different teams for further trail design in the Study of SAS® LSAF (Display 12).



Display 12. Import Study metadata from Define-XML

Finally, the Define-XML generated by Nicardipine Study comes out. From the Define-XML generated by SAS® LSAF, we can see that it's fully compliance with the same style sheet as CDISC Define-XML sample. (Display 13 VS. Display 10).

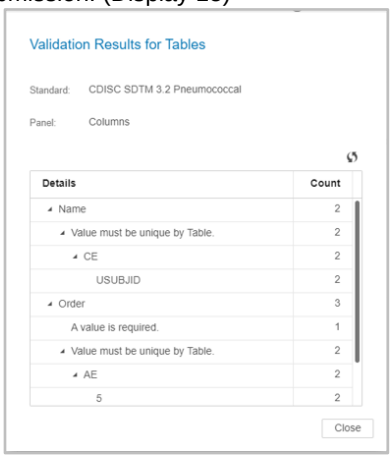


Display 13. Define-XML generated from SAS® LSAF

VALIDATION

During editing and generating submission in the Study, SAS® LSAF supports validation by directly button-click-by to validate your metadata per CDISC validation rules. Any metadata not following CDICS rules can be listed and with the detailed reason in the Validation dialog (Display 14). Furthermore, to handle batch of validation error, warning and

notes, we also support to export validation results as the report of.csv file. The validation, the relationship, and the traceability can be checked in the validation report, this provided the standardized and validated Define-XML for submission. (Display 15)



Display 14. Validation in SAS® LSAF

	A	B	C	D	E	F	G
1	Validation Results						
2	Standard name: SDTM 3.1.2						
3	Current standard state: Development (In Progress)						
4	Published state:						
5	Published version: -						
6	Errors: 0 Warnings: 2 Notes: 199						
7	June 8, 2019 1:38:18 AM GMT by Emma						
8							
9	Severity	Object Type	Domain	Column	Column Group	Attribute	Problem
10	WARNING	Data Standard	DM				The required domain DM for this standard was not found.
11	WARNING	Data Standard	TS				The required domain TS for this standard was not found.
12	NOTE	Column Template		DTYPE	AnalysisDescriptor	Core	Undefined value Cond for column Core.
13	NOTE	Column Template		AELLT	CodingVariable	Core	Undefined value Cond for column Core.
14	NOTE	Column Template		AEHLT	CodingVariable	Core	Undefined value Cond for column Core.
15	NOTE	Column Template		AEHLGT	CodingVariable	Core	Undefined value Cond for column Core.
16	NOTE	Column Template		AESOC	CodingVariable	Core	Undefined value Cond for column Core.
17	NOTE	Column Template		SMQzzNAM	CodingVariable	Core	Undefined value Cond for column Core.
18	NOTE	Column Template		SMQzzSC	CodingVariable	Core	Undefined value Cond for column Core.
19	NOTE	Column Template		CQzzNAM	CodingVariable	Core	Undefined value Cond for column Core.
20	NOTE	Column Template		TRTEMFL	FlagVariableADAE	Core	Undefined value Cond for column Core.

Display 15. LSAF validation report

From goal 3, we see SAS® LSAF provides the specification that defines the metadata structures of the Define-XML for submission by an easy button click wizard and compliance check validation report. Goal 3 increases the level of automation and improves the efficiency of the Regulatory Review process.

CONCLUSION

Good solutions and tools can help us to handle the complex clinical trial data easily and effective. Besides that, clear process implementation strategy is also the key requirement. SAS® LSAF and SAS® JMP Clinical are the kind of the solutions to help the developers' work in the pharmaceutical area easier, with the centralized repository and SAS development environment; with CDISC standard compliance metadata management Study; with process management and automation analysis report utility tools. These enable us to focus on more creative work. With the combination of SAS® LSAF and SAS® JMP Clinical, analysis in an end- to -end clinical metadata management to submission process becomes more luminous. (Figure 13)

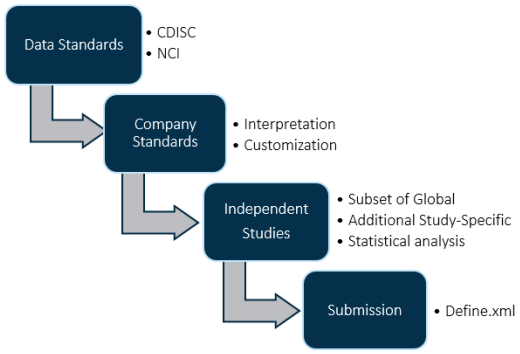


Figure 13. Clinical metadata process

APPENDIX

SAS® LSAF INTRODUCTION

Being as the key leading analytics foundation for clinical research, SAS® LSAF (Life Science Analytics Framework) integrates both information management and analytics in a single solution while seamlessly integrating with the SAS program development and execution environment, complete with CDISC global Standards, study metadata management and workflow capabilities. (Figure 14)

- It ensures regulatory compliance with the controlled validated environment, audit history and robust version controls for managing and change history of files.
- It ensures internal and external collaboration by workflow capabilities in the permission-controlled repository.
- It also ensures reproducibility and traceability SAS programing works by Job and manifest files with to design, run, debug programs.

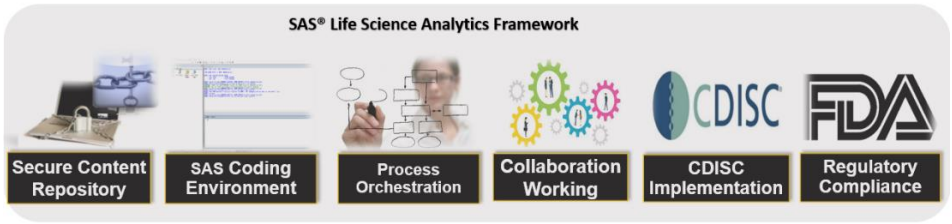


Figure 14. SAS® LSAF Introduction

JMP CLINICAL ANALYSIS REPORTS EXAMPLE

1. Medical writers (PATIENT NARRATIVES)

Producing adverse event narratives for clinical study reports (CSRs) can be a painstaking, time-consuming process with significant consequences for inaccuracies or delays. JMP Clinical enables medical writers automatically combine patient profiles and patient narratives and generate rtf to reduce the time and complexity of creating output for review and submission to regulatory agencies. Figure 15 shows adverse event narratives of Nicardipine with the sample data in Nicardipine Study, we can see the Adverse Events with the concomitant medications and laboratory test Results base on each unique identifier Subjects ID. From the plot, Subject 51002 got the Severe Adverse Events of Subarachnoid Haemorrhage with the concomitant medications of Phenobarbital. From tables view (Figure 16), we can see detailed information of each AE events, the Action Taken with Study Treatment, the Dose of Concomitant Medications during Start End date/time periods per Subject.

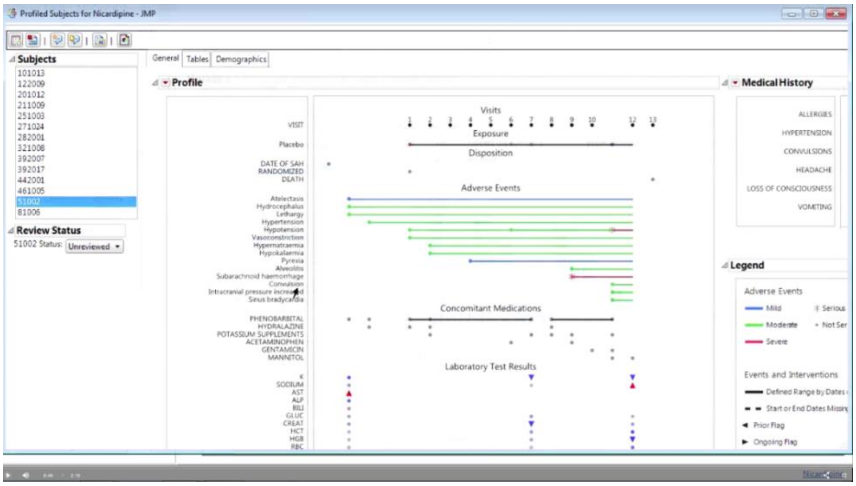


Figure 15. Profiled Subjects for Nicardipine

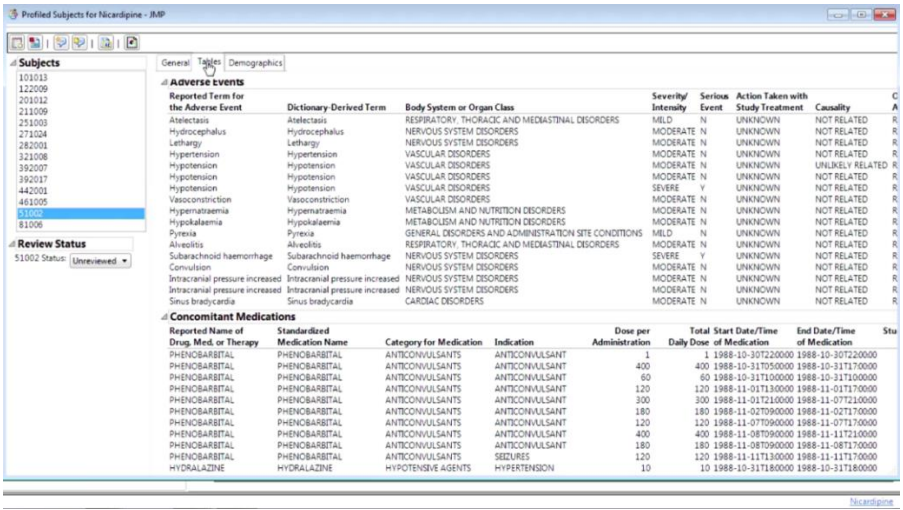
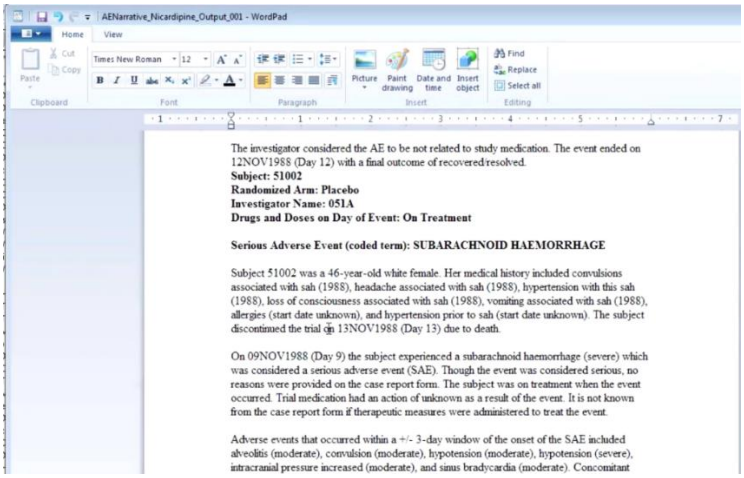


Figure 16. Profiled Subjects for Nicardipine Tables view

Generates rtf File - According to above AE narratives for clinical study reports with Nicardipine sample data. JMP Clinical supports generate rtf file which contains narratives as the one below (Display 16). The rtf report illustrates the SAE (Severe Adverse Event) of subarachnoid haemorrhage to be not related to study medication. Subject 51002 was 46-year-old white female with the Randomized Arm by Placebo, her medical history shows a series of symptoms of the Severe Adverse Event of Subarachnoid Haemorrhage in 1988, Subject 51002 discontinued the trail on 13NOV1988 due to death. Though the event was considered to serious, but no reasons were provided on the case report form. The subject was on treatment when the event occurred, but the Action Taken with Study Treatment has an unknown result of the event, so that the investigator considered the SAE to be not related to study medication.



AENarrative_Nicardipine_Output_001 - WordPad

The investigator considered the AE to be not related to study medication. The event ended on 12NOV1988 (Day 12) with a final outcome of recovered/resolved.
Subject: 51002
Randomized Arm: Placebo
Investigator Name: 051A
Drugs and Doses on Day of Event: On Treatment

Serious Adverse Event (coded term): SUBARACHNOID HAEMORRHAGE

Subject 51002 was a 46-year-old white female. Her medical history included convulsions associated with sah (1988), headache associated with sah (1988), hypertension with this sah (1988), loss of consciousness associated with sah (1988), vomiting associated with sah (1988), allergies (start date unknown), and hypertension prior to sah (start date unknown). The subject discontinued the trial on 13NOV1988 (Day 13) due to death.

On 09NOV1988 (Day 9) the subject experienced a subarachnoid haemorrhage (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. The subject was on treatment when the event occurred. Trial medication had an action of unknown as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a +/- 3-day window of the onset of the SAE included alveolitis (moderate), convulsion (moderate), hypotension (moderate), hypotension (severe), intracranial pressure increased (moderate), and sinus bradycardia (moderate). Concomitant

Display 16. Rtf of AE narratives

Per above example, we see JMP Clinical compose a configurable patient narrative for each subject who experienced an Adverse Event (AE), including reporting for deaths, serious AEs, AEs of special interest and AEs resulting in study discontinuation. It generates rtf to reduce the time and complexity of creating output for review and submission to regulatory agencies.

2. Researchers (Tumor Response Analysis)

In Tumor Response Analysis, JMP clinical can quickly identify efficacy signals in solid tumor clinical trials using visualizations tailored to RECIST criteria. Figure 17 summarizing tumor burden for measured lesions by study visit. This process uses the TR, TU (optional), and RS (optional) oncology domains to create Spider Plots showing tumor results and Waterfall Plots showing Best or Last recorded responses. Measurements in the plots represent change or percent change of tumor burden from baseline in measurable/target lesions. For direct lesion measurement tests such as LDIAM or DIAMETER, lesions are summed and compared to the baseline lesion summation by study visit or study day in Nicardipine Study.



Figure 17. Tumor Reponse

Waterfall Plot -Waterfall Plot shows the “best” percent change in overall tumor burden1 relative to the baseline for each subject that occurred during the study period. Bars above baseline represent overall tumor growth, bars below baseline represent overall tumor shrinkage. Bar color corresponds to treatment. Subjects who show no change in tumor size are represented by a + symbol on the plots instead of a bar. From the report we can easy to compare the tumor burden percentage change between Treatment A and Treatment B

Spider Plot-Spider Plot shows the percent change in tumor size relative to the baseline for each subject at each visit over the course of the Nicardipine Study. Spider plots may also be annotated with new lesions or selected

3. Clinical Operations (Risk-Based Monitoring)

To monitor the data quality of Nicardipine Study, the role of clinical operations in pharmaceutical organization plays big part. Our goal is to mitigate data quality risks that could hinder a regulatory submission or drug approval. Risk-based monitoring tools in JMP Clinical can help clinical operations identify data anomalies at the vendor, monitor, site and country level, and determine the factors responsible for lapses in safety or data quality. JMP Clinical provides analysis reports on Site-Level Distribution, Site-Level Maps, Country-Level Distributions and Country-Level Map. We can run Risk Based Monitoring in the Nicardipine Study of JMP Clinical to generate the comprehensive reports directly. In this section, we will introduce examples in Site Level Risk Indicators, Site-Level Distribution and Site-Level Maps.

Site Level Risk Indicators - From Figure 18, we can see that by choosing different risk Indicator, we can validate our clinical data regarding Site-Level Risk easily. It's easy to tell the Over All Risk Indicator in each Study Site across different countries including the Overall Risk Indicator Safety, Screen Failure, Percent Screen Fail of Total, and so on.

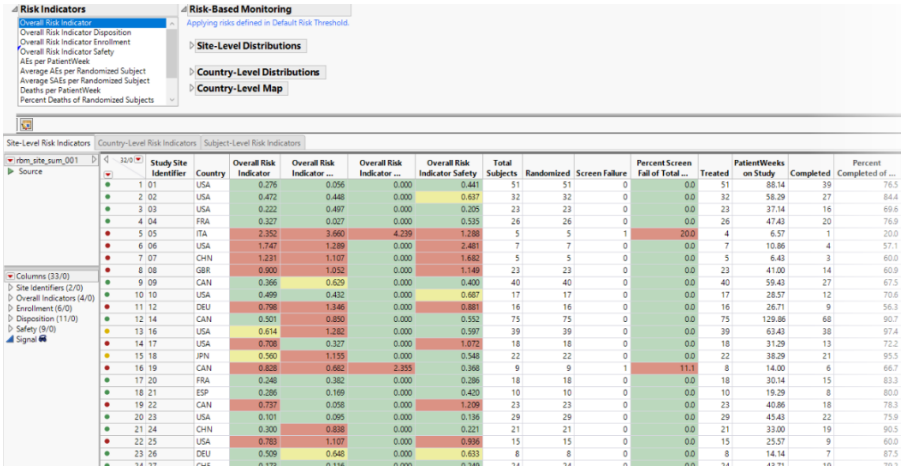


Figure 18. Site-Level Risk Indicator

Site-Level Distribution including a set of Histograms for variables grouped by Nicardipine Study Site Identifiers, Overall Indicators, Enrollment Metrics, Disposition, Adverse Events, and Manually-Entered Site Metrics. It enables you to view the distribution of risk indicators across sites, possibly identifying any outliers. The color of outliers is based on the risk indicator selected from the Risk Indicators down. (Figure 19, Figure 20)

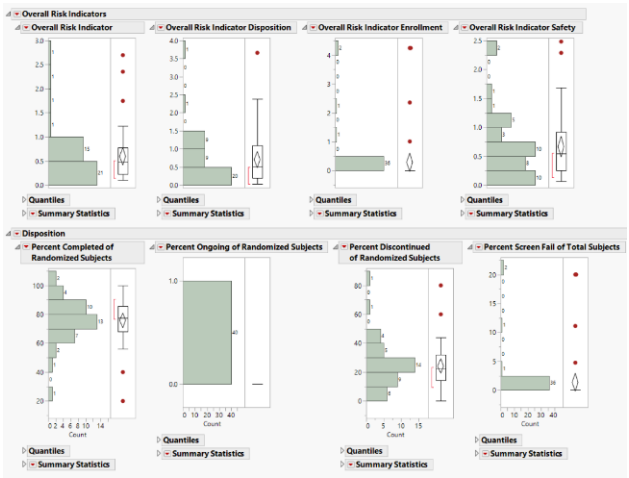


Figure 19. Site-Level Distribution against Overall Risk and Disposition

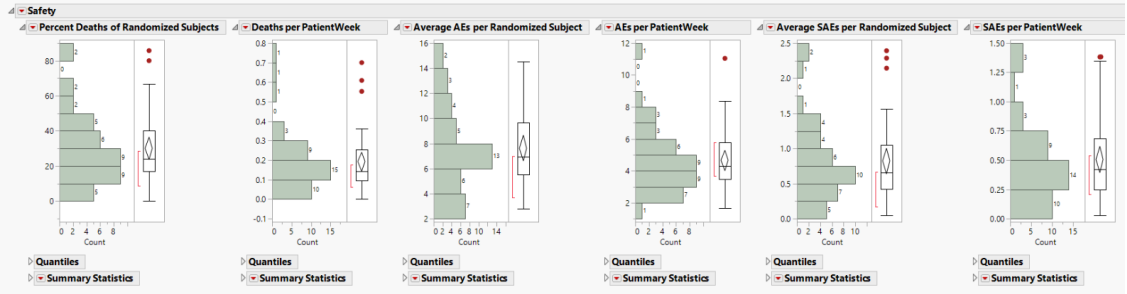


Figure 20. Site-Level Distribution against AE and SAE

Site- Level Maps contains global and, depending on the countries present in the data, country maps detailing the location of the clinical sites based on geocoding. Site colors are based on the selected risk indicator (Figure 21).

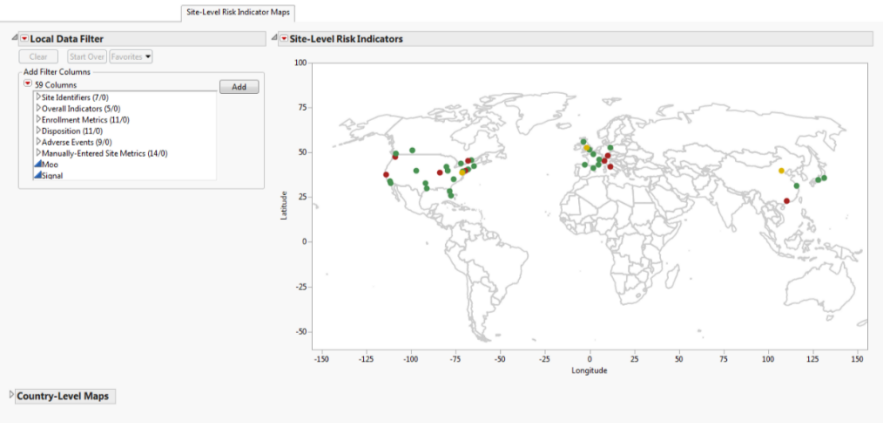


Figure 21. Site-Level Risk Indicator Maps

From above Risk-Based Monitoring reports, it's easy to tell that JMP Clinical reduces costly on-site source data verification while preserving data integrity and the safety of study participants. JMP Clinical can discover data anomalies at the site and patient level, whether due to fraud, data quality or protocol errors.

REFERENCES

- SAS® Life Science Analytics Framework 5.1: User's Guide
- JMP Clinical: User's Guide

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