

The background is a dark blue gradient with a subtle pattern of small white dots. Overlaid on this are several faint, light blue geometric elements: concentric circles, arcs, and a large circular scale with tick marks and numbers ranging from 140 to 260. Some of these elements have small arrows indicating a clockwise direction.

NEXT GEN SHINY APPLICATION FOR REGULATORY SUBMISSIONS

JAYASHREE VEDANAYAGAM, APPLIED STATISTICIAN, PRINCEPS TECHNOLOGIES INC

AGENDA

- INTRODUCTION
- APPLICATION DETAILS
 - ANALYSIS INPUTS
 - ANALYSIS DISPLAY
 - DATA EXPLORER
 - INFERENCIAL STATISTICS
 - eSUB DOCUMENTATION
- ADDITIONAL DETAILS
 - FUTURE ENHANCEMENTS
 - VALIDATION
 - AUDIT TRIAL AND TRACKING
- CONCLUSION

INTRODUCTION

Innovative methods are explored to make regulatory submission process faster, efficient and with quality. One such method is shiny application and dashboard. It is user-friendly, reproducible and scalable.

Understanding Standards & Guidelines

- CDISC Standards
 - SDTM IG
 - ADAM IG
 - TAUG
 - Analysis Results Standards
- FDS Conformance Guideline and ISS, ISC Guidelines for CTD
- EMA ICH Guidelines on CTD

R Packages and R shiny application

- R is widely used and open source software for Data Science, vast package library
 - Tidyverse, ggplot2, Haven – Data processing
 - Rmarkdown, Kniter, Kable – Report rendering
 - Survival, Hmisc, Epitool – Statistics
- Application in R
 - Shiny – R, CSS, HTML
 - Shinydashboard, shinycssloaders
 - plotly

APPLICATION DETAILS

ANALYSIS INPUTS

- Variable Identification & Subset
- **Grouping variables:** row variable and column variables (discrete vars).
- **Treatment variable** identifier (per CDISC ADaM IG) topmost column variable.
- **Data subset** : population subset, analysis subset and BigN/Denominator subset.
- **Dependent variable** : identified into discrete or continuous analysis and appropriate analysis statistics
- **Type of report** is simply whether it is table or figure.

The screenshot shows the top navigation bar of the 'Clinical Analysis Results Visualization Ensemble' application. It includes a 'Load Data' button with a 'No file selected' status, a 'Process Input' button, and a 'Download' button. A dropdown menu is open, showing options: 'Analysis Report' (highlighted), 'Data Explorer', 'eSUB Documents', 'Profiling', and 'Documentation'. Below the navigation bar, there is a section for 'Analysis Inputs' with a 'Report Type' dropdown set to 'Table'. On the right side, there are input fields for 'By Variable Label', 'Statistics Label', and 'Report Titles'.

This screenshot shows two input fields for subsetting conditions. The first field is labeled 'analysis Subsetting Condition' and the second is labeled 'Denominator Subsetting Condition'. Both fields are currently empty.

This screenshot shows a dropdown menu for 'Dependent/Analysis Variable **' and an input field for 'Statistics Displayed'. The dropdown menu is currently empty, and the 'Statistics Displayed' field is also empty.

This screenshot shows two input fields for group variables. The first field is labeled 'By Group Variables' and the second is labeled 'Sub Group Variables'. Both fields are currently empty.

This screenshot shows a dropdown menu for 'Report Type'. The menu is open, showing three options: 'Table' (selected), 'Table', and 'Figure'.

This screenshot shows a dropdown menu for 'Analysis Inputs Report Type'. The menu is open, showing a list of options: 'Figure' (selected), 'Bar Chart', 'Line Plot', 'Boc Plot', 'Error Bar', 'Scatter Plot', 'Histogram', and 'Step Plot'.

APPLICATION DETAILS

ANALYSIS DISPLAY

- viewing results – Table/ Figure
- customizing title/footnote
- saving the report. (3 formats pdf, html and docs)
- Grouping vars for figures : column variable becomes faceting and row variable is value filter.
- Default title footnote is generated based in the variable label attributes that come along with data
- Reactable or datatables for listings

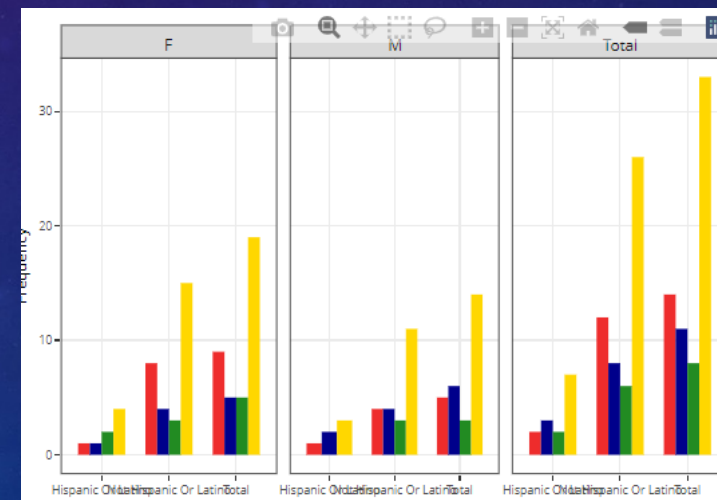
Age Group		Placebo (N=56)			Xanomeline High Dose (N=54)		
		F (N=53)	M (N=33)	Total (N=86)	F (N=40)	M (N=44)	Total (N=84)
<65	HISPANIC OR LATINO	1 (1.16%)	1 (1.16%)	2 (2.33%)	1 (1.19%)	2 (2.38%)	3 (3.57%)
	NOT HISPANIC OR LATINO	8 (9.30%)	4 (4.65%)	12 (13.95%)	4 (4.76%)	4 (4.76%)	8 (9.52%)
	Total	9 (10.47%)	5 (5.81%)	14 (16.28%)	5 (5.95%)	6 (7.14%)	11 (13.10%)
65-80	HISPANIC OR LATINO	0	0	0	0	0	0
	NOT HISPANIC OR LATINO	22 (25.58%)	20 (23.26%)	42 (48.84%)	28 (33.33%)	27 (32.14%)	55 (65.48%)
	Total	22 (25.58%)	20 (23.26%)	42 (48.84%)	28 (33.33%)	27 (32.14%)	55 (65.48%)
>80	HISPANIC OR LATINO	1 (1.16%)	0	1 (1.16%)	0	0	0

By Group Variables

AGEGR1

AGEGR1

<65



APPLICATION DETAILS

DATA EXPLORER

- This is to enable doing basic data check
- Understand available variables and values.
- Generating simple listings.
- Viewing selected variable as data table and applying subset
- Variable attribute, distinct values and check for missing can also be done.
- Additional features : minimalistic statistics planned to be included

Select Variables to be viewed

USUBJID

TRT01P

AVDOD

CUMDOSE

AGEU

SAFFL

BMIBLGR1

Column visibility

Search

	USUBJID	TRT01P	AVDOD	CUMDOSE	AGEU	SAFFL	BMIBLGR1
1	01-701-1015	Placebo	0	0 YEARS	Y		25-30
2	01-701-1023	Placebo	0	0 YEARS	Y		>=30
3	01-701-1028	Xanomeline High Dose	77.7	13968 YEARS	Y		>=30
4	01-701-1033	Xanomeline Low Dose	54	756 YEARS	Y		25-30
5	01-701-1034	Xanomeline High Dose	76.9	14067 YEARS	Y		25-30
6	01-701-1047	Placebo	0	0 YEARS	Y		>=30
7	01-701-1097	Xanomeline Low Dose	54	10260 YEARS	Y		25-30
8	01-701-1111	Xanomeline Low Dose	54	540 YEARS	Y		<25
9	01-701-1115	Xanomeline Low Dose	54	2970 YEARS	Y		<25
10	01-701-1118	Placebo	0	0 YEARS	Y		<25

Showing 1 to 10 of 254 entries

Previous

1

2

3

4

5

...

26

Next

Select Variable to see distinct values

DCDECOD

Column visibility

	DCDECOD
1	COMPLETED
2	ADVERSE EVENT
3	STUDY TERMINATED BY SPONSOR
4	DEATH
5	WITHDRAWAL BY SUBJECT
6	PHYSICIAN DECISION
7	PROTOCOL VIOLATION
8	LOST TO FOLLOW-UP
9	LACK OF EFFICACY

Showing 1 to 9 of 9 entries

APPLICATION DETAILS

INFERENCEAL STATISTICS

- This has endpoint specific analysis and advanced methods
 - Confidence interval
 - p value
 - risk analysis
 - Hypothesis testing
 - T test
 - advanced regression models
- These report structure would be analysis specific

Risk Ratio

Risk Ratio

Risk Difference

Control Group

☒ Placebo

☐ Xanomeline High Dose

☐ Xanomeline Low Dose

Treatment Group

☒ Xanomeline High Dose

☐ Xanomeline Low Dose

	Placebo	Xanomeline High Dose	Risk Ratio (CI)
NERVOUS SYSTEM DISORDERS	12 (17.39%)	27 (34.18%)	1.965 (1.08,3.58)
DIZZINESS	2 (2.9%)	12 (15.19%)	5.241 (1.22,22.6)
HEADACHE	7 (10.14%)	6 (7.59%)	0.749 (0.26,2.12)
SOMNOLENCE	2 (2.9%)	1 (1.27%)	0.437 (0.04,4.71)

	TP LSmean (SE) (N=38)	Control LSmean (SE) (N=18)	Difference	
			95% CI	P-value
Primary Analysis (MMRM)	-1.7 (0.9)	-4.7 (1.2)	3.0 (0.1, 6.1)	0.04
Supportive Analyses*				
MMRM	-2.8 (1.0)	-4.9 (1.4)	2.2 (-1.2, 5.5)	0.21
ANCOVA (Control-Median)	-2.4 (0.9)	-4.9 (1.3)	2.6 (-0.7, 5.8)	0.12

Just for illustration, Not yet included in application

APPLICATION DETAILS

eSUB DOCUMENTATION

- Defines
- SDRG and ADRG
- Combined analysis reports
 - The combined report are produced in pdf, html and doc formats.
 - interactive plotly object in html format is created.

Metadata

- ADaM / SDTM Specifications
- Code lists



```
write_define {defineR}
```

```
write_define(  
  path,  
  dir,  
  type = "sdm",  
  ver = NULL,  
  check = TRUE,  
  html = TRUE,  
  view = TRUE,  
  report_type = "PDF",  
  end_char = ""  
)
```

Section Selection Field:

- Introduction
- Protocol Design
- Analysis Dataset Relationship



1. Selection of list of dataset
2. Description
3. Mock shell / combined reports
4. Issues and details



1. Generating LoT
2. Markdown template
3. Spec and Metadata inputs

ADDITIONAL DETAILS

FUTURE ENHANCEMENTS

- Report layouts recommendation,
- improved SDRG/ADRG docs,
- implementation of CDISC analysis result standards,
- Incorporating biomedical concepts.
- There is also a trial participant level report
- This is also explored in the application by using patientProfileVis and patientProfiler R packages.
- Additionally report specific input capture is also included for traceability.

ADDITIONAL DETAILS

VALIDATION

- Test scripts are created using testthat functionalities for individual utilities.

```
library(testthat)
expect_identical() # checks for exact equality (values, attributes and type of the objects)
expect_equal() # checks for equality with numerical tolerance (values and attributes only)
expect_equivalent() # more relaxed version of equals (values only)
expect_error() # checks that an expression throws an error
expect_warning() # checks that an expression gives a warning
expect_output() # checks that output matches a specified value
```

➤ Shinytest2

- Unit Tests
 - Server Function Tests
 - Snapshot-based test
- shinyload test are explored for application testing.
 - Record
 - Replay
 - Analyze

ADDITIONAL DETAILS

AUDIT TRIAL AND TRACKING

- Tracking documents and audit trail system to ensure compliance.
- Generating program/application logs.
 - Logger
 - Shiny Log
 - Logr
 - logrx
- If the application is hosted on a dedicated study area this implementation becomes much easier e.g. AWS S3
 - Aws.s3
 - Aws.ec2metadata
 - Aws.signature

```
Sys.setenv(AWS_DEFAULT_REGION = "us-east-1")
username <- <Enter the user name>
password <- <Enter the password>
rolearn <- <arn:aws:iam::555316523483:role/####-###-###-##-###>

use_credentials()

Bucket_Name<--<Enter the bucket name>
bucket_details<-get_bucket(bucket = Bucket_Name)|
```

```
## Write object to S3B
s3write_using(tempdata,
              FUN = saveRDS,
              object = "CDISC/ADaM/ads1.Rds",
              bucket =Bucket_Name)

## Read Data from S3B
AnalysisData<-s3read_using(FUN=readRDS,
                           bucket = Bucket_Name,
                           object="CDISC/ADaM/ads1.Rds")

## Delete object in S3B
delete_object(object = "CDISC/ADaM/ads1.Rds",
              bucket=Bucket_Name)
```

CONCLUSION

Interactive R shiny applications and dashboards provide us interactive user interface to create analysis results with capability of embedding data and metadata documentation; therefore, they might be an efficient future option for regulatory submissions.

THANK YOU! QUESTIONS?
