Which Paint Brush Shall I Choose-- Mapping out Your Visualization Plan for Clinical Studies

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ABSTRACT

During a clinical study, there are a lot of aspects that we want to see and investigate. Often throughout the process, the visualization needs involve multiple functions including medical affairs, pharmacovigilance, regulatory, publishing, data management and clinical operations etc. Each function has their own way of displaying and understanding the results of a trial.

In this paper, we will first discuss the needs by each function of our internal clients by breaking down their needs by analysis level, timeliness and display format. Secondly, we will map the software tools according to these needs from our setting. The third part we will discuss about as programmers how to manage the painters' box so you have your paint brushes ready when requests come in like a storm. In the last part we will talk about what visualization means and what it will become in the future.

INTRODUCTION

We are in a small team of onsite programmers where our programming team works in a one-shop-serves-all mode. That means we cover all the requests from Pharmacovigilance, Marketing, Medical Affairs, Regulatory, Publication and company executives. Knowing the final piece of work you are going to draw is very helpful when you are deciding to pick the right brush for it.

As programming and data analysis function, it is very necessary to think carefully on the existing programming tools we have for clinical graphics and establish a strategy to better serve our internal clients. Various tools including SAS® Graphics , JMP®, Graph Template Language(GTL), ODS Graphics Designer and SAS Visual Analytics® will be discussed in this paper to map out the best way to collaborate and serve different purpose during a clinical trial study visualization needs in our settings.

Disclaimer: This is personal view only, does not represent Santen's view.

WHAT OUR INTERNAL CLIENTS WANT

Here is a personal summary after interviewing many of our colleagues:

GRAPHS IN SUBMISSIONS

The SAS programming function in pharmaceutical industry mainly supports study submission. Thus the submission package graphs are a big chunk of the visualization work. As regulatory agency publishes their standard on submission package, it is very predictable to plan the graph programming for the efficacy endpoint analysis and different statistical analysis. From my work, I categorized several kinds of graphs and their purposes in the submission packages.

Purpose of the Graph	Type of the Graph
Efficacy Endpoint	Can be line plot, bar chart, boxplot, forest plot etc.
Safety Endpoint	Same as above, usually a line plot will serve the purpose fine.
Time to Event	Kaplan-Meiver survival plot, time plot, water fall plot etc.
Showing the Accuracy of a Trial	ROC curve etc.

Table 1. Categories of graph types and their purpose in the submission package

Timing of the programming of these graphs is planned according to submission project timeline. The output format requirement is also very predictable as the agency publishes eSubmission standards. It is recommended to check with your publishing team about the standard fonts, formatting and arrangements of the pages.

For example, the FDA NDA package does not like color figures. The function of a figure in the submission is not to show off the results in a fancy way but to demonstrate the fact of the study. Nor does the FDA require user interactivity as they are not the ones who will explore the study hand in hand with you. The FDA would want a clean, firm and accurate answer from the trial. Thus I rated the graph needs as the following:

✱✱✱✱✱	Time Urgency Requirement
✱✱✱✱✱	User Friendliness
✱✱✱✱✱	Display Complexity
✱✱✱✱✱	Format Standaridzation

A good brush to use in this case would be SAS® Graphics plus GTL. For example, we can use SAS Graphics SGPLOT to create figures with macro-driven high-low range from the data and use GTL to handles the final display of the graphs.

PRE-CLINICAL

Our pre-clinical scientists have the needs of displaying pre-clinical experiments results fast and in a standard format. Their opinions are vital part of the go-no-go decision for a candidate compound. Different from a clinical trial, pre-clinical animal trials usually have smaller sample size, various designs and usually a shorter lifecycle.

Moreover, our pre-clinical scientists would want to explore the data in different dimensions such as mapping out each data point and looking into outliers of an experiment. It would be very necessary to have a tool that is easy to use (point and click) and equipped with flexible and interactive data selection function. Here I rated pre-clinical visualization needs as below:

✱✱✱✱✱	Time Urgency Requirement
✱✱✱✱✱	User Friendliness
✱✱✱✱✱	Display Complexity
✱✱✱✱✱	Format Standaridzation

As there is no strict formatting requirement by our pre-clinical team, I think some tools like JMP® would be a very good visualization environment for this stage. Users can get choose the graph display style without much programming language. All the built-in statistical models and graph template can quickly show a combination of graphs together. The feature of showing subgroups in parallel is extremely helpful for our scientists to choose between compounds. I believe the two most favorite traits are the compatibility with Microsoft® Excel and the highlighted data points from graphs.

CLINICAL OPERATIONS

The visualization needs of Clinical Operations lies mostly in clinical trial risk-based monitoring. Within the ongoing trial process, they will need the results of the site performance fast and accurately so as to fix the issues quickly. These following parameters are what attract attention of Clinical Operations, and sometimes data management as well.

Purpose of the Graph	Type of the Graph
Site Performance Monitoring (Open Query Rate, Screen Failure Rate, Early Termination Rate, etc.)	Pie chart for displaying rate in % Bar chart for comparing different sites
Site Efficiency (Data Key-in Time, Query Cycle Time etc.)	Heat map for comparing among sites

Table 2. Categories of graph types and their purpose for Clinical Operations

✱✱✱✱✱	Time Urgency Requirement
✱✱✱✱✱	User Friendliness
✱✱✱✱✱	Display Complexity
✱✱✱✱✱	Format Standaridzation

It is usually the above key factors that drive the monitoring of trial site performance. The timeliness and user-friendliness of the visualization software mean a lot to our Clinical Operations end users. There are various tools in this field. Spotfire® is one of the mainstream visualization tools that Clinical Operations use. There are custom-built algorithms and also point- and-click displays. While exploring the flexibility of self-customized monitoring algorithms,

we find SAS® Visual Analytics can provide real-time interactive display as well as automatic workflow that can notify the end user by emails.

DATA MANAGEMENT AND PHARMACOVIGILANCE

As you might already know, Data Management and Pharmacovigilance monitor clinical data on a day to day basis as well as Clinical Operations.

We serve these two departments by detecting and displaying the data issues and event of interests within ongoing data during the study. The timely fashion is much appreciated. You cannot image how much hassle it saves for the whole process to work magically together. There are mainly two kinds of outputs that involved graphs:

Purpose of the Graph	Type of the Graph
Patient Profile, Data Tabulations	Can be line plot, bar chart, and series plot by subject level
Timeline graphs	Visualize events by study day, e.g., Sanjay Matange's AE+CM graph

Table 3. Categories of graph types and their purpose for Data Management and Pharmacovigilance

We found guru Sanjay's Combined AE +CM timeline graph very useful in helping our Pharmacovigilance colleagues understanding the subject level safety portfolio.

�✶✶✶✶	Time Urgency Requirement
✶✶✶✶	User Friendliness
✶✶✶	Display Complexity
✶✶✶✶	Format Standaridzation

What kind of tool can provide large batch of graphs in fast speed and on a daily basis in this case? We think SAS® Graphics on SAS® Life Science Analytic Framework (LSAF®) together with LSAF Extension platform is able to schedule the jobs from run pulls from Medidata® server to output to end users for daily review.

MEDICAL AFFAIRS, MARKETING AND EXECUTIVES

Medical affairs, marketing and executives are people who communicate the key findings of a clinical trial to the external world. They want the graphs to carry accurate and strong messages.

The expectation is usually a summary slide that contains key findings of the study. Usually a fancy version of efficacy endpoint is provided in a PowerPoint form. Marketing might want demographic map by disease severity to find out which region and subgroup of population to target to.

- A fancier version of key endpoint findings (with a touch of PROC SGPANEL, GTL)

Besides the key findings, our end users would love to have interactive display for example where the data filter can be adjusted. Furthermore, there might exploratory findings such as combining historic data and show the comparison in panels, or compare with other published trial data or among subgroups etc.

- Exploratory outputs (interactive tools such as SAS® Visual Analytics, ODS Graphics Designer etc.)

✶✶✶✶	Time Urgency Requirements
✶✶✶✶	User Friendliness
✶✶✶✶	Display Complexity
✶✶	Format Standaridzation

For our demanding executives, how can we have the fancy look as quick as possible, meanwhile everything has to be accurate and well-documented? What if our Medical Affair colleagues find something very important to present to KOLs? I found two shortcuts for data visualization here. One is to upgrade the submission package using a "fancy" version of style library or GTL. The other is to use ODS Graphics Designer to explore results interactively and save the converted SAS codes. This provides good documentation for exploratory figures as they can be later upgraded to more official outputs if necessary.

THE PAINT BRUSH ORGANIZER

We have now get aquantied with all our painting brushes as we mapped the tools from submission package to exploratory adhocs. What are some of the tips that help us organize the painting box?

As we all are somewhat habitual, there is a continuity on the software that people choose to use.The cost of maintaning, training of people (espeically for the new end users) and how the software can be brought across the board plays almost equally important role as the software performance itself.

It is always good to keep a table of content on your graph library and what might be needed to update or convert the existing figures in some other forms . For example, as we disucssed in the last section of our internal clients discussion, we upcycled the submission endpoint for excecutive adhocs. It will take a lot more efforts to create the figure from scratch. Thus creating a knowledge pool of study specific graphic library would be very helpful.

Another tip is not to overdevelop. Don't forget that quick and dirty tools are for quick and dirty works. Graphs in Excel sometimes work magically for nonformal requests especially if the source data is already in Excel format.

Here is a very subjective map of what I see in the painter's box:

Internal Clients	Timing	Analysis Level	Display Format	Tools	Tasks
Submission (Regulatory and Publication)	Fixed and predicable, after Data Base lock	High	RTF,PDF	SAS Graphics (GTL)	Endpoints and key findings
Pre-clinical	On-going with Preclinical trials	Medium	Excel and any image format is OK	JMP	Pre-clinical results
Clinical Operations	Before and during the study, Real-time	Low	Excel	SAS Visual Analytics	Data quality, Site monitoring Subject Profile
Pharmacovigilance	During the study, Real-time	Low	RTF,HTML,Excel	SAS Graphics (LSAF)	Safety Profile, AE+CM time series
Medical Affairs	Dates of	Medium	RTF, PowerPoint Slides	ODS Graphics Designer, SAS Graphics	Key results communicated to KOL
Executive Team	Flexible and as quick as possible	High	PowerPoint Slides, HTML	ODS Graphics Designer, SAS Visual Analytics	Key study results, interactive exploratory finding
Marketing	End of submission	Medium	PowerPoint Slides	ODS Graphics Designer, SAS Visual Analytics	Geographic and demographic prediction

Table 4. Summary map of visualization needs

SOME EXTRA THOUGHTS

After putting all these in to the following summary table, I was amazed at how we look at clinical trial and its limitation. We were digitizing the information collected and displaying in pixels. Now the results are redisplayed in a form that the audience will accept. So we did this by standardization of data and see efficacy by comparison. What if the audience is not that visual? Can we display the sound of people's pulse and do pulse reading. Pushing it forward one step, will we be able to reorganize the "raw" information in a more digested form and display the truth not only visually but also for every senses? What if people can sense the results of a clinical trial that they can figure out a way how to cure themselves?

CONCLUSION

I believe there is not one thing fits all in mapping the software to the tasks. It is a very exploratory exercise for a programmer to think out of the box and in the end users shoes to approach the question of how we could best display the clinical trial facts. The choice of software could be totally up to the portfolio of the cost, user acceptance or timing of a study. I hope this paper serves an initiating role of throwing out a minnow to catch a whale by getting more programmers thinking about all the alternatives visualization tools we can use and integrate. It will be awesome to continue this discussion and know everybody's experiences about this topic.

REFERENCES

Matange, Sanjay. "A Combined AE + CM Graph using SAS." PharmaSUG 2017 Available at
https://www.pharmasug.org/proceedings/2017/DV/PharmaSUG-2017-DV02.pdf

ACKNOWLEDGMENTS

RECOMMENDED READING

- Clinical Graphs Using SAS®

- http://sas-and-r.blogspot.com/p/graphics-examples.html

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