Interactive TLFs - A Smarter Way to Review your Statistical Outputs

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ABSTRACT

In the clinical industry, the data is represented and analyzed in the form of tables, listings and figures (TLFs) which are typically generated using SAS®. For the Biometrics team, plotting data and presenting statistical information using SAS ODS and SAS procedures is not new. However, the output that is generated using SAS ODS and SAS procedures are for the most part static and only gives end users an ability to "look" at the output without giving them an ability to explore and drill-down further. With the rapidly increasing availability of data visualization and analytic tools, the industry landscape is shifting. In addition, the end users now want to 'see' their data more interactively, identify trends, visualize the patient profiles and review results at a high-level while still being able to drill-down to get a complete picture. In this paper, we will talk about how we have used the power of SAS and TIBCO Spotfire®, to build "Interactive TLFs" using SDTM datasets to meet these demands. We will demonstrate through a case-study how a clinical team can use this platform to review safety statistical outputs/TLFs (e.g. demographics, disposition, AEs, concomitant medications, laboratory and vital signs) more interactively and thereby avoiding to flipping through hundreds if not thousands of static pages.

INTRODUCTION

In the clinical industry, the data is represented and analyzed in the form of tables, listings and figures/graphs (TLF or TLG) which are typically generated using SAS® in the RTF and/or PDF formats. The clinical study team relies on their Biometrics function (Biostatistics and Statistical Programming) to produce the Clinical Study Report (CSR) TLFs and any data listings/patient profile for their review prior to database lock (DBL) and at least once post-DBL. The Figure 1 below shows us a typical data flow where all TLFs are generated using SAS and the statistical outputs are in RTF and/or PDF formats ("Static TLFs"). For the Biometrics team, plotting data and presenting statistical information using SAS ODS and SAS procedures is not new. However, the statistical outputs that is generated using SAS ODS and SAS procedures are for the most part static and only gives end users an ability to "look" at the outputs without giving them an ability to interact with it.
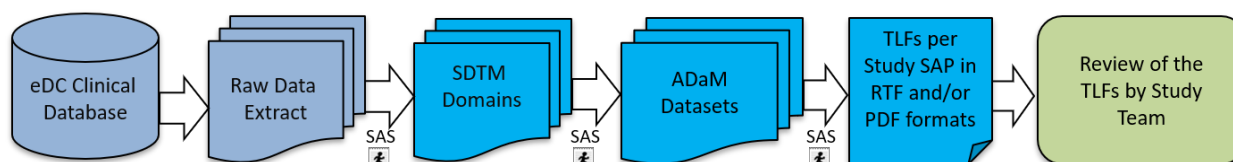

Figure 1: Typical flow of data and statistical outputs for CSR TLFs using SAS ("Static TLFs")

For instance, in the Figure 2 example below, if a Clinician or Medical Writer reviewing the output *Summary of Treatment-Emergent Adverse Events (TEAE)* would like to know more about the two subjects with Serious Treatment-emergent AE in Xanomeline High Dose treatment arm, he or she have to flip through the *Listing of SAE* to identify those subjects and get their underlying data. The review process of flipping through the static summary table and the respective listing/patient profile does get tedious and adds lot more time to the already stringent review cycle.

In this paper, we would like to introduce readers about the possibility of using other analytics tools to provide your study team an ability to 'see' their data more interactively, identify trends, visualize the patient profiles and review results at a high-level while still being able to drill-down to get a complete picture. The intention is to not challenge the process and data flow described above, but rather to challenge the status quo of doing things the traditional way and educate stakeholders about the technology solutions as proposed in this paper that can help clinical study teams make their CSR TLF review and monitoring activities faster and better.

Please note that for the regulatory submission purposes and publishing of the TLFs into the CSR, the Biometrics function will still need to generate the TLFs using SAS.
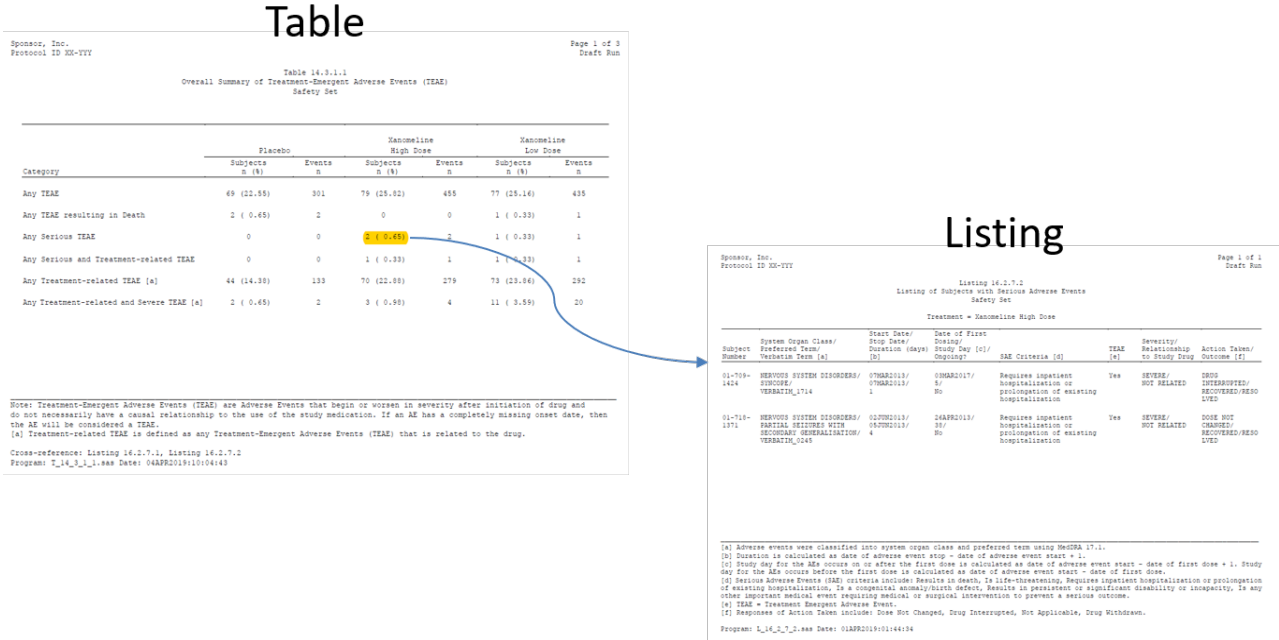
Figure 2: SAS-generated statistical outputs in RTF format.

INTERACTIVE TLFs VIA SPOTFIRE

There are various options for data analytics and visualization tools in the market today. We at Vita Data Sciences (VDS) chose to go with TIBCO Spotfire as our preferred analytics tool because it met most of our needs and requirements. We continue to use SAS for the purpose of data mapping and transformation needs and to utilize it for the generation of the study CDISC datasets and CSR TLFs as well.
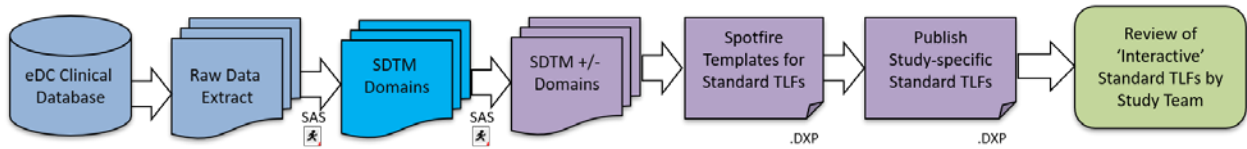

Figure 3:Flow of data to generate standard TLFs for interactive review via Spotfire

The study-specific Spotfire analysis file (DXP file) can be published onto a Web player, where the study team can review TLFs interactively. Spotfire Consumer (previously called as a Web Player) is a powerful tool for sharing and distributing information within and outside an organization. It is a web browser-based application, which requires no installation, and can be used inside a portal or a web site [1, 2]. Web player lets you to filter data, drill down to details, identify spots or trends and export data.

With the power of both the tools, SAS and Spotfire, our team is able to build a robust data analytics and visualization solution to provide our clients with an opportunity to drill-down through multiple levels of detail to aid in their TLF review cycles. The solution is providing our internal team and our clients with an ability to review standardized safety TLFs for an entire study in a more systematic manner. In addition to the graphical representation of the study data, our dashboard also supports following standard safety tables:

- Demographics Summary
- Disposition Summary
- Adverse Event - Overall Summary
- Adverse Event - by SOC and PT Summary
- Concomitant Medications Summary
- Vital Signs Summary by Visits and Change from Baseline
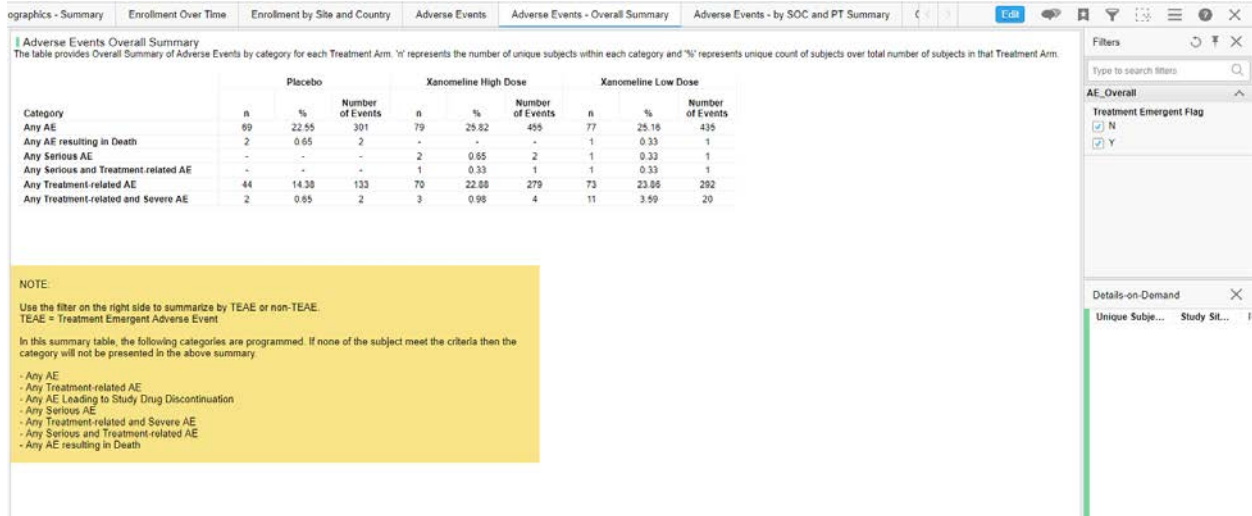- Laboratory Summary by Visits and Change from Baseline

Figure 4:Adverse Events Overall Summary table generated in Spotfire

The Figure 4 above provides a summary of Adverse Events by Treatment Arm. For this table, we used SDTM AE domain and generated *AE_Overall* dataset in SAS before uploading it onto Spotfire for summary purpose. The summary statistics is performed within Spotfire. The idea behind using SAS is to avoid data manipulation and transformation within Spotfire. The advantage to that is for us to be able to QC SAS generated outputs.
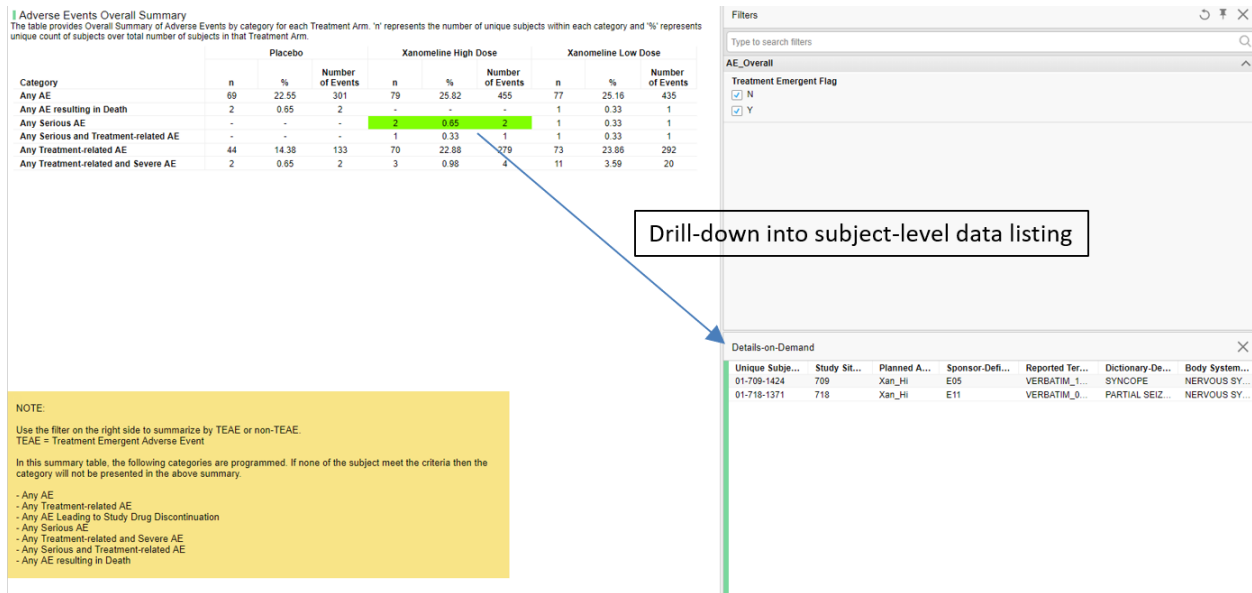
Figure 5:Adverse Events Overall Summary table generated in Spotfire, indicating drill-down capability to get Subject-level data in the Details-on-Demand window.

The Figure 5 above shows how at any point reviewer can get access to underlying Subject-level data by simply marking the cell of interest. The underlying source data of the marked cell can be viewed in the Details-on-Demand panel. In this example, the reviewer can quickly access data from two subjects with Serious Treatment-emergent AE in Xanomeline High Dose treatment arm. The Figure 6 below shows the expanded view of the Details-on-Demand panel presenting the underlying source data of the table in Figure 5. This functionality can be used to drill down into specific details and the data rows can be exported into CSV format for further review and reporting purposes.
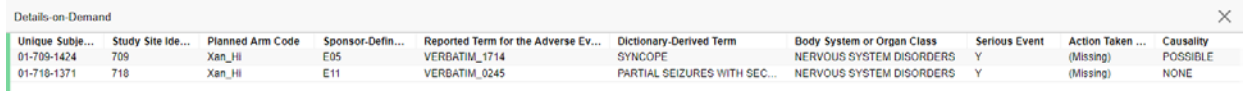

Figure 6: Expanded view of the Subject-level data in the Details-on-Demand window per the marking selected in Figure 5.

Furthermore, the columns in the filter section can be used for sub-setting data and dynamically update the table. When one uses a filter, the values in the data table are filtered out, and only the filtered values, that is the remaining values, are included in what is being summarized. In Figure 7 below, only subjects >= 65 years and treatment arm (Xanomeline High and Low Doses) are included in the updated summary tables. The counts, percentages and number of events are updated based on the selected filtered values.
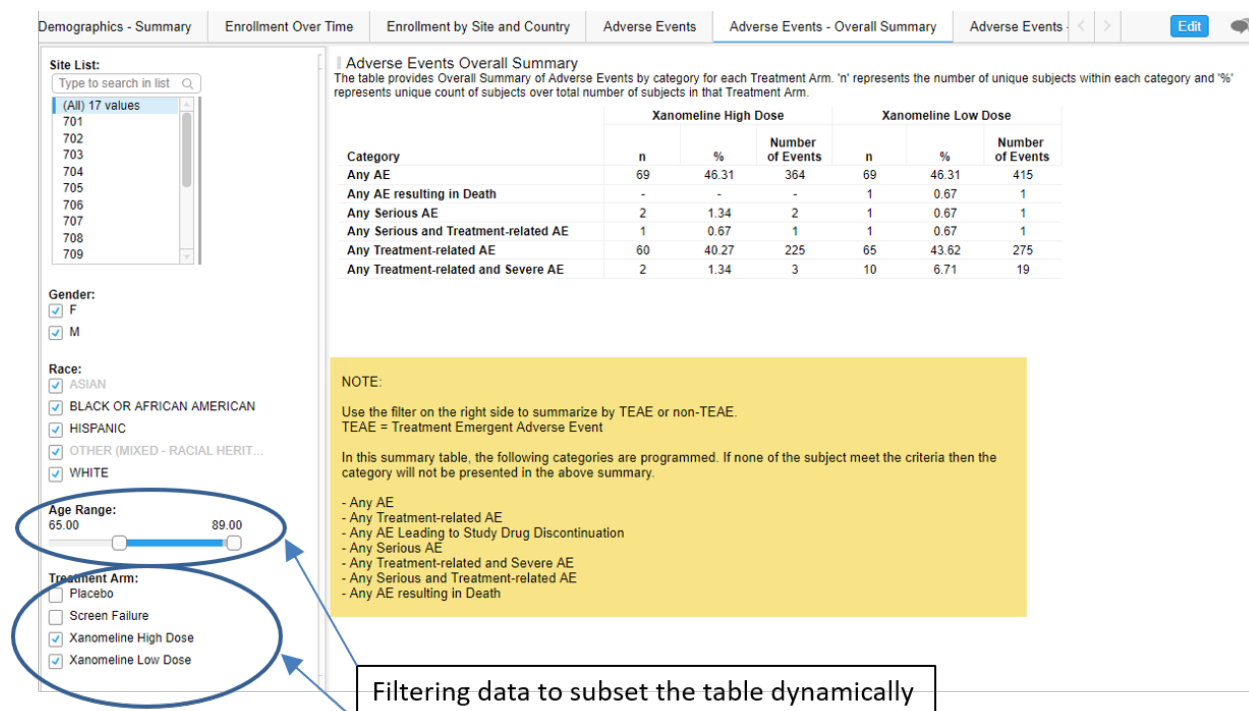

Figure 7: Updated Adverse Events Overall Summary table in Spotfire per the filtered data

With the combination of SAS and Spotfire, we are able to:
- Continue to leverage our current SAS programming expertise towards data mapping and transformation
- Integrate with the current business process, data standards, and analytics environment
- Utilize advance visualization features to interact, identify, review and visualize study data with ease
- Support publishing of TLFs on the web for end users to access via Spotfire Consumer license
- Collectively review TLFs in one central platform
- Export summary tables/visuals effortlessly in form of CSV, PDF, or Microsoft PowerPoint
- Navigate between summary level and subject level details
- Generate patient profile, both graphical and in listing format
- Flexibly change analysis elements by using data filters
- Select or 'mark' data and/or subject(s) of interest
- Link the summary tables/visuals from one page to the other

KEY RECOMMENDATIONS AND LESSONS LEARNED

Based on our experience and several case studies, we have summarized some of the key recommendations and lessons learned:
- Challenge the status quo of doing things the traditional way and educate stakeholders about the technology solutions as proposed in this paper that can help study teams make their data review and monitoring activities faster.
- Implementation of any new tool in the organization requires upfront investment to set-up the infrastructure, and processes. The organization (vendor or sponsor) will need to build a dedicated team and resources to support their data analytics needs.
- Develop and maintain standard requirements, global templates and workflows for data visualization ("out-of-the-box" solution). This will be key to maintain consistency and make the process more efficient/cost-effective. The team can re-use the templates from study to study and client to client. Of course, anticipate customization for each study/client and ensure additional effort/budget is built-in to the project plan to cover the study-specific requirements.

- In our proposed data flow, we are recommending the use of SDTM +/- for data analytics and visualization; this requires additional programming efforts. However, given we typically also work on generating SDTM datasets for the study, the programs can be used for both Data Analytics and Statistical Analysis purposes. Utilizing SDTM will result in reusability, faster ramp-up time, and will maintain consistency.
- Although the process could be automated, we do recommend adding a layer of QC upon each refresh of the data for an on-going study. In addition, if the source data is mapped or transformed, the programming validation and QC process should be followed.
- Ensure all end-users are trained on each study-specific data visualization instance. Add a disclaimer that the data represented in tool such as Spotfire is for the data review, exploratory and monitoring purpose only. Data Analytics tools should not be used for any regulatory and/or publication purposes.

CONCLUSION

In this paper, we talked about how we have used the power of SAS and TIBCO Spotfire®, to build "Interactive TLFs" using SDTM datasets. We demonstrated by providing specific example how a clinical study team can use this platform to review safety statistical outputs/TLFs (e.g. demographics, disposition, AEs, concomitant medications, laboratory and vital signs) more interactively and thereby avoiding to flipping through hundreds if not thousands of static pages. In addition, the user can review and analyze the data collaboratively by publishing the results to the study team members. Moreover, we can utilize the collaboration tool within Spotfire to comment on the analysis state or any specific data points. Lastly, the user is able to export any summary tables/visuals or underlying source datasets effortlessly in form of CSV, PDF, or Microsoft PowerPoint.

REFERENCES

[1] TIBCO Spotfire® Business Author and Consumer User's Guide.
https://docs.tibco.com/pub/sfire-consumer/7.9.0/doc/html/en-US/GUID-6CF74B7C-9425-4BDE-B8C4-F9F45B1F1710.html

[2] TIBCO Spotfire® Business Author and Consumer User's Guide.
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