PhUSE 2015

Paper TT10

# Future Drug Applications with No Tables, Listings and Graphs?

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## ABSTRACT

Moving into the digital era, the endless piles of tables, listings and graphs (in PDF) could be history.

We analyze data electronically in SAS®, and the TLGs are still in the same typewriter format – electronic, but must be printable. Hundreds of pages are prepared to 'summarize' the findings for one trial. This makes any reviewer of the results exhausted.

Introducing CDISC, we are moving towards a digital environment, but we should take steps to become fully digital. This would ease the burden of the reviewer and minimize the effort and cost of reporting a trial.

Being digital, we should present the results by using visualizations. Should it not be possible to summarize the key results from a clinical trial in 30-50 visualizations as a sort of executive summary? Using a tool like JMP® Clinical (or similar) could bring us the first step away from the endless pile of summary TLGs.

## INTRODUCTION

Moving into the digital era, the endless piles of tables, listings and graphs (in PDF) could be history.

When I entered the pharmaceutical industry in the mid-'90s data was collected on paper, double-entered into a database, analyzed in SAS® on mainframe or PC, and Tables, Listings and Graphs (TLGs) were created to summarize the results. Those were appended to a report, printed and filed in a binder. Today, we have only come a small step away from that process and in some areas made it even worse.

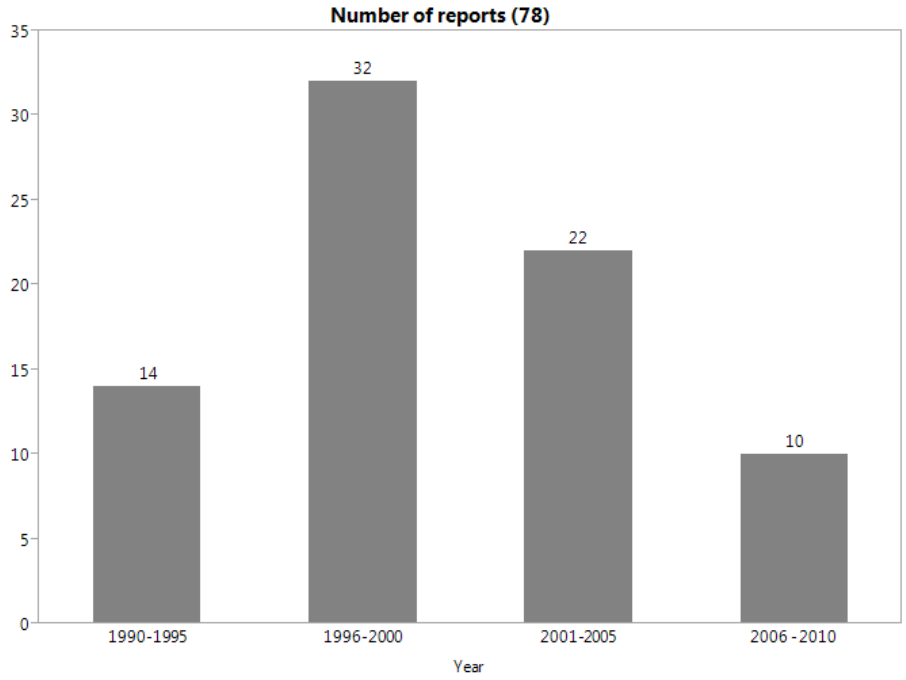
### REPORTING AS WE KNOW IT

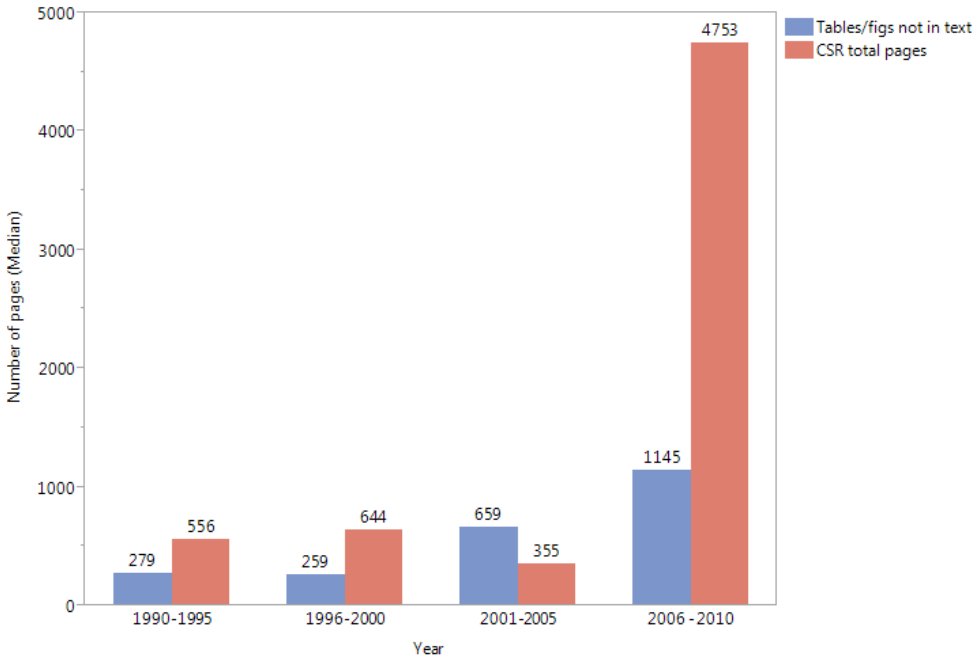
We collect data electronically, but we still make annotated CRF in PDF when a submission is prepared. We analyze data electronically using the procedures in SAS, and the TLGs are still in the same typewriter format – electronically, but must be printable if needed. We have transformed the 'paper world' into the 'digital world', but not really reaped the benefits and possibilities that digital media provide. Initially, it was probably what was possible at that time, but today, with everything being digitized, it is time to let go of the old paper world paradigm and become fully digital.

In addition, due to this paper world thinking, it seems that there is a trend to make clinical trial data results into 'big data'. Hundreds, if not thousands, of pages are made to 'summarize' the findings just for one trial.

To illustrate this trend, I reused data collected for the article: *Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports*, by Peter Doshi and Tom Jefferson [1.]. The purpose of their article is to illustrate what a CSR contains. The authors have permitted me to use the data to illustrate the trend in volume.

A sample of 78 reports was obtained with the following distribution over time (top) and the median number of pages over time (bottom):




Based on the sample of 78 reports, the number of pages both in end-of-text (blue bars) and the Clinical Study Report (red bars) is increasing. The increase in pages can to some extent be ascribed to the increase in required data to be collected. Nevertheless, this trend makes any reviewer of the results exhausted.

As a reviewer, how do you get an overview of the data by looking at piles of tables like Table 1? Is this an efficient way to transform data to knowledge? A reviewer will probably need several tables and graphs in the table to get the overview.

Table AE 3
Incidence of Treatment Emergent Adverse Event by System Organ Class, Preferred Term, and Treatment
(Format 2)
All Randomized Subjects

| Body Class or System Organ Class | Preferred Term | Placebo N=xxx | Demo Dose 10 mg N=xxx | Demo Dose 30 MG N=xxx | Demo Dose 60 MG N=xxx |
|---|---|---|---|---|---|
| With Any Adverse Event | Overall | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| SOC Term 1 | | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 1 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 2 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 3 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| ... . | | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| SOC Term 2 | | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 1 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 2 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 3 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| ... . | | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| SOC Term 3 | | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 1 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 2 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| | Preferred term 3 | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |
| ... . | | xxx (xx) | xxx (xx) | xxx (xx) | xxx (xx) |

Note: denominator of percentage is the number of subjects in the column
Percentage is based on the number of subjects who had event not the number of events.

**Table 1 Traditional AE table in TGLs section**

## IMPROVING BY INTRODUCING STANDARDS

By introducing CDISC standards and the use of define.xml, we are moving towards a more digital environment. Using the CDISC data standards as the norm enables development of tools to support review of data.

Tools are on the market today that support review of the CDISC data, but we still make a very large amount of TLGs in PDF when reporting a trial.

If we could take steps to become fully digital, this would ease the burden of the reviewer and probably minimize the effort and cost of reporting a trial.

## FUTURE CLINICAL RESULTS IN VISUALISATIONS

Being fully digital, we should move towards presenting the results using visualizations. Should it not be possible to summarize the key results from a clinical trial in 30-50 visualizations as a sort of executive summary? All the basic summaries and listings can be extracted from the visualization tools. Using a tool like JMP® Clinical (or similar tools) could bring us the first step away from the endless pile of summary TLGs.

By using traditional data presentation as in Table 1 above, a reviewer would need to oversee several tables to get an overview of the AEs in a study. In the interactive report as in Table 2 below, the reviewer can get 3 different illustrations (the 3 tabs in the top: counts graph, counts table and distribution) and have the ability to filter, drill down and view the underlying data in a very simple way using the filters to the left.

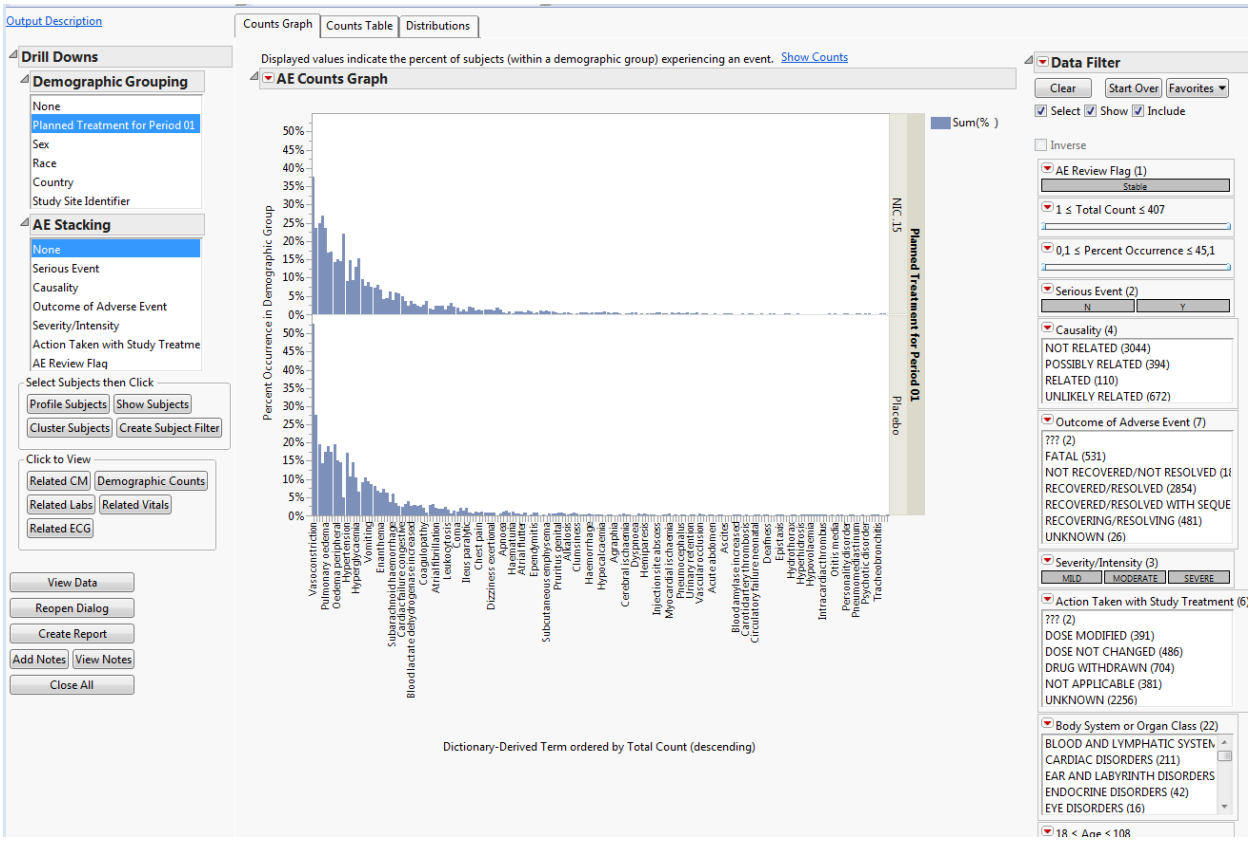



**Table 2 Interactive AE table in visualization using JMP Clinical**

In this tool (JMP Clinical), a 'review journal' can be made to document the sponsor's side of the story, and access to the SDTM, SEND and ADaM is providing the reviewer full access to perform any analysis.

## HOW DO WE GET THERE?

It seems very tempting to switch into data visualizations, but being in a regulated environment and the fact that data visualizations are still new in the pharmaceutical industry gives us challenges that we need to overcome.

But, imagine a future where a trial report has no PDF – or at least limited to very few pages. What would we need to get there?

- Like the dataset XML initiative for exchanging datasets, we need some standard exchange format for data visualizations that can be read by different tools. This will also require some metadata definitions of data visualizations. E.g., how does a tool know how to read a bar chart, a table or a volcano plot?

- An integrated Clinical Metadata Repository where all standards can be defined and managed in a machine-readable format, e.g. SEND, SDTM and ADaM model definitions, Controlled Terminology, validation rules. These definitions must be shared in the tools used to define and describe the clinical trial and its outcome. The CDISC SHARE initiative is a good step in this direction. The machine-readable standard should then be imported/read by the visualization tools.

- Protocol (and statistical analysis specifications) to be in a machine-readable format. The number of tools on the market to generate this is very limited. The only tools that I am aware of are Excel and Medidata Designer.

- Data Collection Specifications in machine-readable format, including the ability to link to the CDISC SDTM data. Tools like Business Decision & Life Science's CDMation, XClinical's StudyComposer and Formedix's Origin have some of the functionality, but not all data is collected in a traditional CRF. More data sources are used, e.g. Questionnaires and Patient Devices, and it must be able to link to the SDTM data from a shared Metadata Repository as explained above.

- Extension and improvement of the visualization tools (JMP Clinical as an example shown above) to accommodate SEND data and to provide a fully digital analytical report of the data and the full use of ADaM datasets.

- Consider how the traditional Clinical Trial Report is going to look in a digital environment. The eCTD is a structure to start from, but tools are needed and a complete rethinking of the concept is required.

- The skills to create digital reports and the ability to understand and use the visualizations. Creation of the reports seems to be the competencies of a data scientist, but the users and reviewers need to be trained in understanding the output.

- Most important is it that all the regulatory agencies are to accept a digital report like this. This requires some guidelines on what to submit and in which format. In addition, the agency reviewers need to be trained in digital reviewing.

Most likely, more issues need to be solved that I have not thought of.

## CONCLUSION

So, is this a crazy idea? I hope not. The world around us is becoming more and more digital and adaption to new technologies is happening very fast – also within health care – so why should the pharmaceutical industry be different?

There is still a way to go before we are able to become completely digital. First step is to set a common vision and to initiate pilots to test it. Maybe it could be a topic for a new PhUSE CS Working Group.

As previously mentioned, I believe that data visualizations would ease the burden of the reviewer and probably minimize the effort and cost of reporting a trial. Who knows, maybe even getting better review of the data and thereby better drugs faster to the patients?

In addition, it will support transformation of data into knowledge, i.e. aggregation of data and not disseminating it into thousands of pages of tables. We should exploit the potential of the CDISC standards being required by FDA, PMDA and EMA (once Individual Patient Data is being enforced by EMA).

## REFERENCES

[1.] Doshi Peter, Jefferson Tom. *Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports.* BMJ Open 2013;3.

## ACKNOWLEDGMENTS

Thanks to Peter Doshi and Tom Jefferson for sharing the data on Clinical Trial Reports. Thanks to Puni Rajah for providing valuable comments.

## RECOMMENDED READING

Simon, Phil: *The Visual Organization,* Wiley

## CONTACT INFORMATION

Your comments and questions are valued and encouraged. The author of this paper can be contacted at:

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