

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

PhUSE Annual Conference 2015, Vienna

Kirsten Walther Langendorf

SAS Institute, Denmark



## CURRENT ISSUES Why listen to this presentation?

Output – huge amount for clinical trial reporting



Paper – just electronically



Overwhelmed by producing it or reviewing it

## FUTURE VISION Why listen to this presentation?

Efficiently extract the essence



Digital dynamic reporting of data  
– no (electronic) paper



Better review? – better treatments?

## OUTLINE ... of presentation

- Reporting as we know it
- Future clinical results in visualizations & suggestions on how to get there
- Conclusions

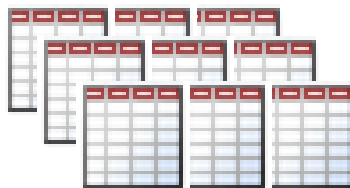
# REPORTING As we know it

eCTD

## Annotated CRF – pdf

|                                                                                                                                                                                                                                                                                                                                                                                          |   |   |   |   |   |   |   |   |                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Subject identification</b> <b>DOMAIN=[DM] [SC]</b><br><br>Subject number: <b>SUBJID</b> <b>BRTHDT</b><br>Date of birth: <table border="1"><tr><td>d</td><td>d</td><td>m</td><td>m</td><td>y</td><td>y</td><td>y</td><td>y</td></tr></table><br>Gender: <input type="checkbox"/> male <b>SEX</b> <input checked="" type="checkbox"/> female<br><b>SCORRES where SCTESTCD="RACEOTH"</b> | d | d | m | m | y | y | y | y | Ethnicity: <b>ETHNIC</b> <input type="checkbox"/> Hispanic or Latino<br><input type="checkbox"/> Not Hispanic or Latino<br>Race: <input type="checkbox"/> Asian<br><input type="checkbox"/> Black or African American<br><input type="checkbox"/> White<br><input type="checkbox"/> American Indian or Alaska Native<br><input type="checkbox"/> Native Hawaiian or Other Pacific Islander<br>Other, specify: _____ |
| d                                                                                                                                                                                                                                                                                                                                                                                        | d | m | m | y | y | y | y |   |                                                                                                                                                                                                                                                                                                                                                                                                                     |

## Study and analysis data – SAS tables and define.pdf/xml




Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment

Table AE 3  
(Former 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                       | 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)              |
| SOC Term 2                       | 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)              |
| SOC Term 3                       | 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)              |

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 ev

# REPORTING As we know it

eCTD

Annotated CRF – pdf

Subject identification DOMAIN=[DM] [SC]

Subject number: SUBJID BIRTHDT

Date of birth: d d m m y y y y

Gender: ☐ male SEX ☒ female

Ethnicity: ETHNICITY Hispanic or Latino  
☐ Not Hispanic or Latino

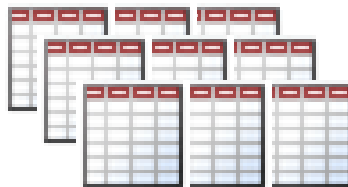
Race: ☐ Asian  
☐ Black or African American  
☐ White  
☐ American Indian or Alaska Native  
☐ Native Hawaiian or Other Pacific Islander  
 Other, specify: \_\_\_\_\_

RACE

SCORRES where SCTESTCD="RACEOTH"

**MUST BE PRINTABLE**

Study and analysis data  
 – SAS tables and define.pdf/xml



Incidence of Treatment Emergent Adverse Events

With Any Adverse Event

SOC Term

Body Class or System Organ Class

Preferred Term

Placebo N=xxx

Demo Dose 10 mg N=xxx

Demo Dose 30 MG N=xxx

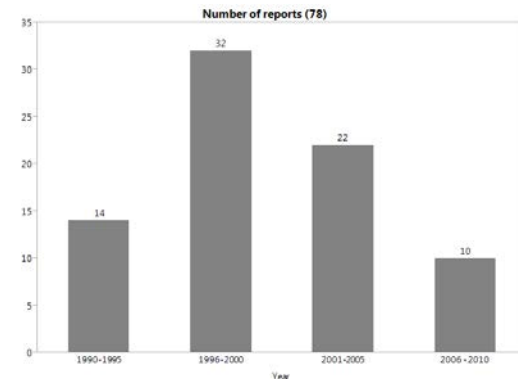
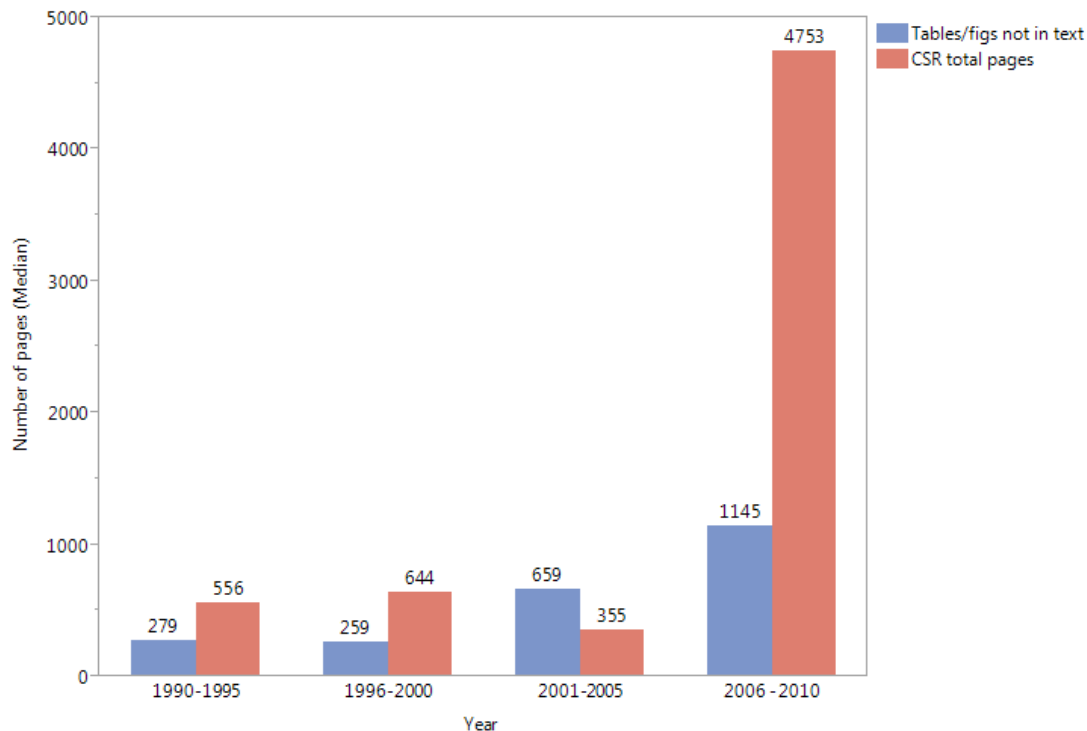
Demo Dose 60 MG N=xxx

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

| SOC Term               | 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             |                                  | 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)              |
| SOC Term 2             |                                  | 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)              |
| SOC Term 3             |                                  | 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)              |

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 ev

## REPORTING Increasing number of (electronic) pages



Data kindly provided by Doshi Peter, Jefferson Tom. *Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports*. BMJ Open 2013;3.

# REPORTING CDISC data standards an opportunity to change

eCTD

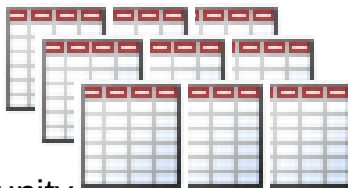
Annotated CRF – pdf

|                                                                                                                                                                                                                                                                                                                                                                                              |   |   |   |   |   |   |   |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Subject identification</b> <b>DOMAIN=[DM] [SC]</b><br><br>Subject number: <b>SUBJID</b> <b>BRTHDT</b><br>Date of birth: <table border="1"><tr><td>d</td><td>d</td><td>m</td><td>m</td><td>y</td><td>y</td><td>y</td><td>y</td></tr></table><br>Gender: <input type="checkbox"/> male <b>SEX</b> <input checked="" type="checkbox"/> female <b>SCORRES</b> where <b>SCTESTCD="RACEOTH"</b> | d | d | m | m | y | y | y | y | <b>Ethnicity:</b> <b>ETHNIC</b> <input type="checkbox"/> Hispanic or Latino<br><input type="checkbox"/> Not Hispanic or Latino<br><b>Race:</b> <input type="checkbox"/> Asian<br><input type="checkbox"/> Black or African American<br><input type="checkbox"/> White<br><input type="checkbox"/> American Indian or Alaska Native<br><input type="checkbox"/> Native Hawaiian or Other Pacific Islander<br><b>RACE</b><br>Other, specify: _____ |
| d                                                                                                                                                                                                                                                                                                                                                                                            | d | m | m | y | y | y | y |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

Study and analysis data  
– SAS tables and define.pdf/xml



Standards enforced – opportunity




Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment

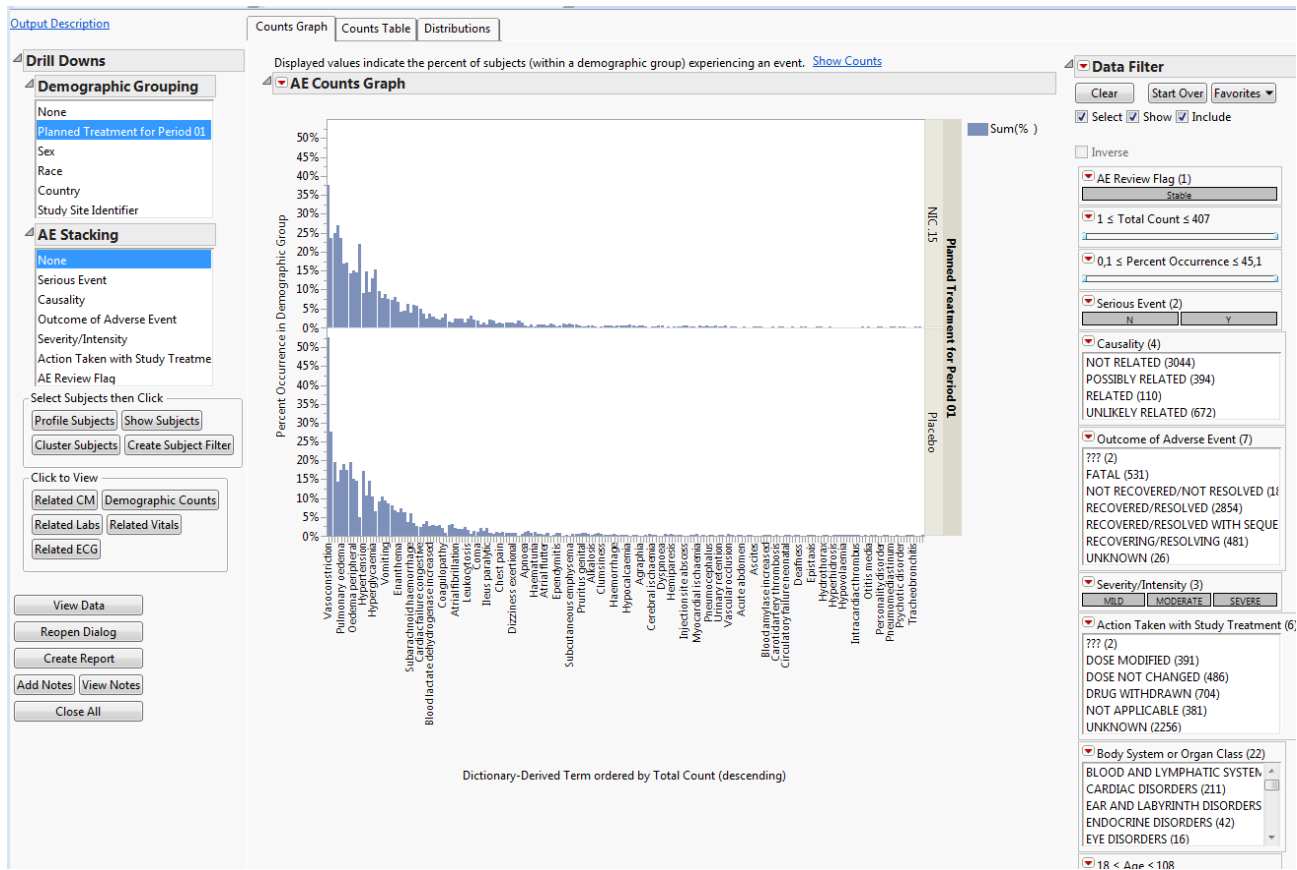
Table AE 3  
Incidence of Treatment Emergent Adverse Event by System Organ Class, Preferred Term, and Treatment  
(Form AE 3)  
All Randomized Subjects

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

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

# FUTURE Clinical results in visualizations

- Dynamic reports
  - Drill down
  - Filtering
  - Profiling
  - Related records



# FUTURE Clinical results in visualizations

- Traditional (but dynamic) tables 'out of the box'
  - Drill down
  - Filtering
  - Profiling
  - Related records

Output Description

Counts Graph Counts Table Distributions

Drill Downs

Demographic Grouping

None  
Planned Treatment for Period 01  
Sex  
Race  
Country  
Study Site Identifier

AE Stacking

None  
Serious Event  
Causality  
Outcome of Adverse Event  
Severity/Intensity  
Action Taken with Study Treatment  
AE Review Flag

Select Subjects then Click

Profile Subjects Show Subjects  
Cluster Subjects Create Subject Filter

Click to View

Related CM Demographic Counts  
Related Labs Related Vitals

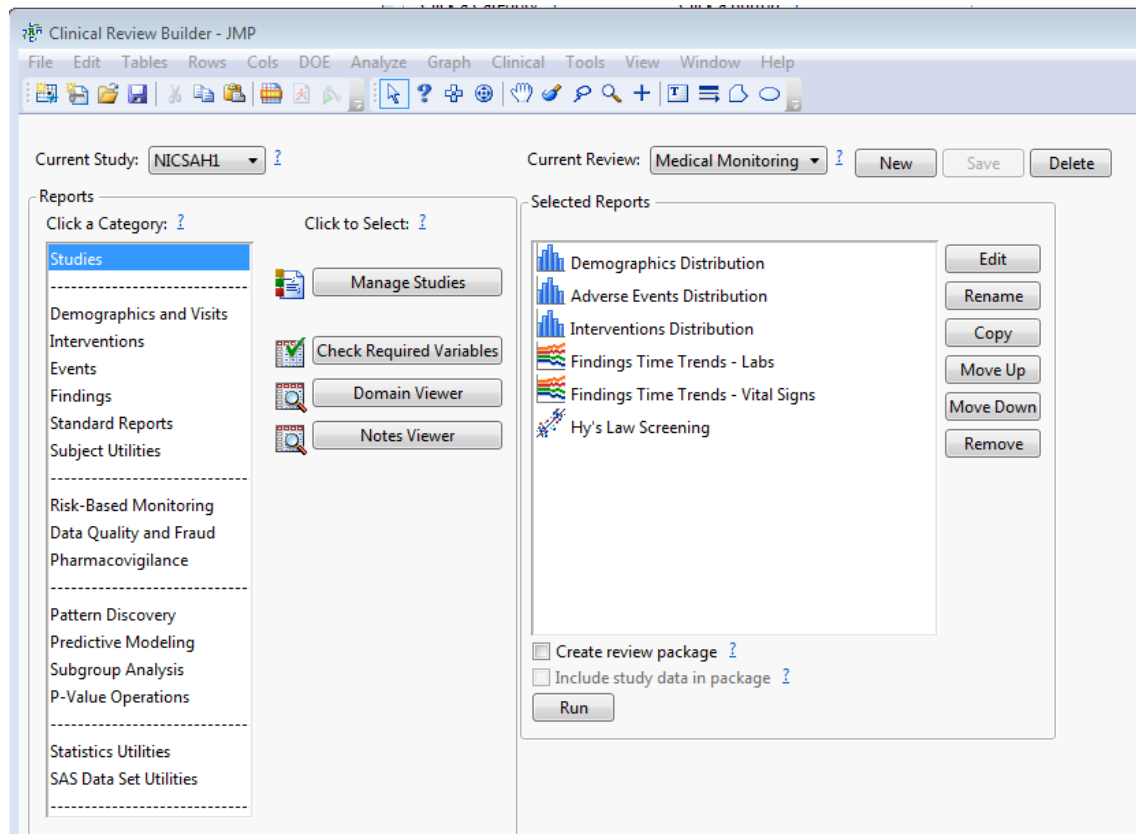
View Data  
Reopen Dialog  
Create Report  
Add Notes View Notes  
Close All

Tabulate

|                                             |                                 | Planned Treatment for Period 01 |       |         |       |
|---------------------------------------------|---------------------------------|---------------------------------|-------|---------|-------|
|                                             |                                 | NIC .15                         |       | Placebo |       |
| Body System or Organ Class                  | Dictionary-Derived Term         | Count                           | %     | Count   | %     |
| VASCULAR DISORDERS                          | Vasoconstriction                | 168                             | 37,6% | 239     | 52,5% |
|                                             | Hypotension                     | 121                             | 27,1% | 65      | 14,3% |
|                                             | Phlebitis                       | 98                              | 21,9% | 23      | 5,1%  |
|                                             | Hypertension                    | 41                              | 9,2%  | 78      | 17,1% |
|                                             | Thrombophlebitis                | 10                              | 2,2%  | 8       | 1,8%  |
|                                             | Vasodilatation                  | 5                               | 1,1%  | 5       | 1,1%  |
|                                             | Haemorrhage                     | 1                               | 0,2%  | 2       | 0,4%  |
|                                             | Vascular occlusion              | .                               | .     | 2       | 0,4%  |
|                                             | Circulatory failure neonatal    | .                               | .     | 1       | 0,2%  |
|                                             | Embolism                        | .                               | .     | 1       | 0,2%  |
| NERVOUS SYSTEM DISORDERS                    | Intracranial pressure increased | 64                              | 14,3% | 89      | 19,6% |
|                                             | Brain oedema                    | 42                              | 9,4%  | 67      | 14,7% |
|                                             | Hydrocephalus                   | 35                              | 7,8%  | 48      | 10,5% |
|                                             | Cerebral infarction             | 34                              | 7,6%  | 39      | 8,6%  |
|                                             | Subarachnoid haemorrhage        | 17                              | 3,8%  | 27      | 5,9%  |
|                                             | Convulsion                      | 13                              | 2,9%  | 13      | 2,9%  |
|                                             | Sinus headache                  | 11                              | 2,5%  | 12      | 2,6%  |
|                                             | Cerebral haemorrhage            | 6                               | 1,3%  | 11      | 2,4%  |
|                                             | Coma                            | 8                               | 1,8%  | 5       | 1,1%  |
|                                             | Dizziness exertional            | 6                               | 1,3%  | 3       | 0,7%  |
|                                             | Lethargy                        | 5                               | 1,1%  | 4       | 0,9%  |
|                                             | Stupor                          | 1                               | 0,2%  | 3       | 0,7%  |
|                                             | Clumsiness                      | 1                               | 0,2%  | 2       | 0,4%  |
|                                             | Agraphia                        | 2                               | 0,4%  | .       | .     |
|                                             | Cerebral ischaemia              | 1                               | 0,2%  | 1       | 0,2%  |
|                                             | Hemiparesis                     | .                               | .     | 2       | 0,4%  |
|                                             | Intention tremor                | 2                               | 0,4%  | .       | .     |
|                                             | Oculofacial paralysis           | 1                               | 0,2%  | 1       | 0,2%  |
|                                             | Pneumocephalus                  | 1                               | 0,2%  | 1       | 0,2%  |
|                                             | Carotid artery thrombosis       | .                               | .     | 1       | 0,2%  |
|                                             | Cerebral hypoperfusion          | 1                               | 0,2%  | .       | .     |
|                                             | Vocal cord paralysis            | 1                               | 0,2%  | .       | .     |
| RESPIRATORY, THORACIC AND MEDIASTINAL DL... | Pulmonary oedema                | 106                             | 23,7% | 80      | 17,6% |
|                                             | Athetosis                       | 76                              | 17,0% | 80      | 17,6% |

## FUTURE Key results from a clinical trial – executive summary

- Sponsors' conclusions
  - 30-50 visualizations
  - Access to the SDTM, SEND and ADaM is providing the reviewer full access to perform any analysis



## HOW ... to get there ?

- Standard exchange format is needed for data visualizations that can be read by different tools
  - Requires 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)
  - Must be shared and used by the tools used to define and describe the clinical trial and its outcome in a standardized way
  - The [CDISC SHARE](#) initiative is a good step in this direction

## HOW ... to get there ?

- Protocol (and statistical analysis specifications) must be in a machine-readable format. The number of tools on the market to generate this is very limited. The only tools I am aware of are Excel and [Medidata Designer](#)
- Data Collection Specifications in machine-readable format – not pdf – 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 this functionality but they generate a pdf (because this is the requirement)
  - 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

## HOW ... to get there ?

- Extension and improvement of the visualization tools (JMP Clinical as an example shown above) to accommodate SEND data and to provide a full digital analytical report of the data and the full use of ADaM datasets
- Consider how the traditional Clinical Trial Report will 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

## HOW ... to get there ?

- The skills to create digital reports and the ability to understand and use the visualizations. Creating the reports seems to be the skills 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 must accept a digital report. This requires some guidelines on what to submit and in which format. In addition, the agency reviewers need to be trained in reviewing digitally.

## CONCLUSIONS Wild fantasy – crazy dream?



## CONCLUSIONS Future Drug Applications with no TLGs?

- 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?
- Data visualizations support the transformation of data to knowledge, i.e. aggregating data and not spreading 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).
- There is still a way to go before we are able to be truly digital. First step is to set a common vision and to initiate pilots to try it out. Perhaps start with the TLGs only. Maybe it could be a topic for a new [PhUSE CS Working Group](#).
- 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 better drugs faster to the patients?

# QUESTIONS Thank you for listening

**Kirsten Walther Langendorf**

Business Delivery Manager ▪ Commercial & Life Sciences

Tel: + 45 70 28 28 70 ▪ Mobile: + 45 51 38 75 42 ▪ [Kirsten.Langendorf@sas.com](mailto:Kirsten.Langendorf@sas.com)

SAS Institute ▪ Koebmagergade 7-9 ▪ DK-1150 Copenhagen K



**SAS® ...THE POWER TO KNOW®**

[www.sas.com](http://www.sas.com)

