CLINICAL STUDY REPORT - IN-TEXT TABLES, TABLES FIGURES AND GRAPHS, PATIENT AND INDIVIDUAL PATIENT DATA LISTINGS: ICH E3 TECHNICAL REQUISITES AND POSSIBLE SOLUTION IN SAS

Data handling and reporting in clinical trials with SAS
Seminario BIAS – Milano 22 / 02 /2013

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Agenda

- Introduction to ICH E3
- Key points in ICH E3 referring to statistical outputs production
- ICH E3 Additional Considerations
- Technical Solutions
  - Software requirements overview
  - In-house solutions
  - Facilitate the work of the medical writer
  - Other possible topics for discussion
- References
Agenda

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Introduction to ICH E3
Structure and Content of Clinical Study Reports (CSR)

- CSRs describe the background, rationale, methodology and full results for a clinical study
- Called *integrated reports* as they cover clinical and statistical aspects
- Guideline ICH E3 on structure and content of CSRs: 53 pages of *guidance*
- Other Guidances
  - ICH E9 Statistical Principles for Clinical Trials
  - ICH M2 EWG The Electronic Common Technical Document (eCTD)
  - FDA Portable Document Format (PDF) Specifications
Introduction to ICH E3
E3 Implementation Working Group Q&A 7 June 2012

- It is a guidance not a set of rigid requirements or a template
- Modifications and adaptations that lead better display and communication of information are encouraged
- Some data in appendices are specific requirements of individual HA and should be submitted as appropriate
- New sections could be added if appropriate
- Repetitions are allowed. E.g. deaths listing vs AE with fatal outcome
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Key points in ICH E3 referring to statistical outputs production

Obviously the TLFs programmed by biostat department are the source of information of CSR

- **In-text tables**: statistical outputs inserted in the body of the CSR, i.e sections 1 to 13 as per ICH E3.
- **End-text**: Section 14: Tables, Figures and Graphs Referred to but not Included in the text. When the statistical output will be presented outside the body of the report
- **Narratives**: detailing deaths, other SAE and significant AE in section 12.3.2
- **Subject/Patients Data Listings**
  - 16.1 Study Information
    - 16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used
    - 16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)
  - 16.2 Patient Data Listings
  - 16.4 Individual Patient Data Listings
Key points in ICH E3 referring to statistical outputs production

The guidance gave also some instructions on the required contents of tables and listings. For example:

- **12.2.4. Listings of Adverse Events** *All adverse events for each patient, ..... should be listed in appendix 16.2.7...the listing should be by investigator and by treatment....and should include: patient identifier, age, race....the adverse event (preferred term, reported term) ...*

- **12.4.2.2. Laboratory Individual Patient Changes** *An analysis of invidual patient changes by treatment should be given e.g. shift tables*

- **Some template for figures, tables and listings are also provided. For example:**
  - Disposition of patients (figure)
  - Listings of patients who discontinued therapy
  - Listings of patients and observations excluded from efficacy analysis
  - Number of patients excluded from the efficacy analysis

The guidance contains also instructions on «expected» statistical analysis to be taken in consideration for the SAP development (see also section 16.1.9)
Key points in ICH E3 referring to statistical outputs production

In-text tables

**Table 1–1  Subject Disposition (Referring to Appendix 15.1 Table 15.1.1.1)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>W (N=62) N (%)</th>
<th>K (N=60) N (%)</th>
<th>I (N=62) N (%)</th>
<th>Total (N=206) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Screened Subjects</td>
<td></td>
<td></td>
<td></td>
<td>206</td>
</tr>
<tr>
<td>Safety Population</td>
<td>61 (98.4)</td>
<td>59 (98.3)</td>
<td>62 (100.0)</td>
<td>182 (88.3)</td>
</tr>
<tr>
<td>ITT Population</td>
<td>62 (100.0)</td>
<td>60 (100.0)</td>
<td>62 (100.0)</td>
<td>184 (89.3)</td>
</tr>
<tr>
<td>Per Protocol Population</td>
<td>45 (72.6)</td>
<td>36 (60.0)</td>
<td>43 (69.4)</td>
<td>124 (60.2)</td>
</tr>
<tr>
<td>Total number (%) of discontinued subjects</td>
<td>60 (96.8)</td>
<td>58 (96.7)</td>
<td>58 (93.5)</td>
<td>177 (85.9)</td>
</tr>
<tr>
<td>Reason For Discontinuation As Randomized</td>
<td>60 (100.0)</td>
<td>58 (100.0)</td>
<td>58 (100.0)</td>
<td>177 (100.0)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>9 (10.0)</td>
<td>10 (19.0)</td>
<td>14 (19.0)</td>
<td>23 (15.8)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (8.3)</td>
<td>7 (12.1)</td>
<td>5 (8.6)</td>
<td>17 (9.6)</td>
</tr>
<tr>
<td>Inclusion And/Or Exclusion Criteria Not Full-filled</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Subject Withdrew Consent</td>
<td>4 (6.7)</td>
<td>3 (5.2)</td>
<td>2 (3.4)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>33 (55.0)</td>
<td>29 (50.0)</td>
<td>33 (56.9)</td>
<td>95 (53.7)</td>
</tr>
<tr>
<td>Symptomatic Deterioration</td>
<td>3 (5.0)</td>
<td>2 (3.4)</td>
<td>1 (1.7)</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Others</td>
<td>9 (15.0)</td>
<td>5 (8.6)</td>
<td>5 (8.5)</td>
<td>20 (11.3)</td>
</tr>
</tbody>
</table>

- RTF output: a **word table** that can be easily inserted into the CSR
- Include **CAPTION** for automatic reference once they are inserted in the CSR
- **Source** should be also mentioned (e.g. post-text table/listing)
Key points in ICH E3 referring to statistical outputs production

Post-text tables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistics</th>
<th>W (N=35) Median (mo) [95% CI]</th>
<th>t (N=62) Median (mo) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumor Site</td>
<td>Oropharynx</td>
<td>11 5.5 [3.1; 6.7] 1.47 [0.62; 3.45]</td>
<td>22 4.5 [4.0; 11.0]</td>
</tr>
<tr>
<td></td>
<td>Hypopharynx</td>
<td>10 6.6 [5.6; 9.5] 1.37 [0.51; 3.73]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral cavity</td>
<td>15 5.7 [1.4; 6.9] 2.13 [0.77; 5.88]</td>
<td></td>
</tr>
<tr>
<td>Tumor Grade</td>
<td>Well or Moderately</td>
<td>46 6.9 [4.3; 5.5] 1.01 [0.57; 1.78]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>differentiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>25 5.6 [4.3; 12.5] 0.75 [0.37; 1.53]</td>
<td></td>
</tr>
</tbody>
</table>

Median: Product-limit (Kaplan-Meier) estimates
Note: Hazard ratio of K or L 2 over t alone.
Note: Randomization strata used for stratification: Karnofsky performance status (from IVRS)

Complex output summarizing information coming from different PROCs e.g. LIFETEST (Median 95%CI) and PHREG (HR 95%CI) to save space and improve readability
Key points in ICH E3 referring to statistical outputs production

Alternative solution can be implemented to avoid split in several pages when there are many information to report. e.g. adverse events listing.

SAS Proc Report

Proc REPORT Tutorial. C. Zender. WUSS 2010
Key points in ICH E3 referring to statistical outputs production

Figures

EMF, EPS, WMF and CGM are recommended file formats

Sponsor Standard Graph Library

Should allow B&W printing without losing any information. Their display should be verified
### Sponsor Patient Profile Tool

**Key points in ICH E3 referring to statistical outputs production**

**Subject Profile**

<table>
<thead>
<tr>
<th>Date of Birth: 12 Jun 1963</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female</td>
</tr>
<tr>
<td>Race: Other, HISPANIC</td>
</tr>
<tr>
<td>Status: End of Treatment: Withdraw Prematurely</td>
</tr>
<tr>
<td>Status: End of Study: Not Completed</td>
</tr>
</tbody>
</table>

**Clinical Study Report - In-text tables, Tables Figures and Graphs, Patient and Individual Patient Data Listings: ICH E3 technical requisites and possible solution in SAS – A. Tinazzi – Seminario BIAS – Milano 22/02/2013**

#### Vital Signs

- **Systolic BP (mm Hg)**
  - Screen: 132
  - SD1: 130
  - SD8: 132
  - SD22: 132
  - Wk 8: 146
  - Wk 12: 102
  - Wk 16: 108
  - Wk 20: 114
  - Wk 26: 120
  - Wk 38: 

- **Diastolic BP (mm Hg)**
  - Screen: 70
  - SD1: 92
  - SD8: 80
  - SD22: 100
  - Wk 8: 80
  - Wk 12: 62
  - Wk 16: 
  - Wk 20: 82
  - Wk 26: 72
  - Wk 38: 

- **Heart Rate (bpm)**
  - Screen: 80
  - SD1: 62
  - SD8: 80
  - SD22: 90
  - Wk 8: 69
  - Wk 12: 86
  - Wk 16: 72
  - Wk 20: 72
  - Wk 26: 74
  - Wk 38: 

- **Temperature (Celsius)**
  - Screen: 36.8°C
  - SD1: 38.8°C
  - SD8: 37.1°C
  - SD22: 37.1°C
  - Wk 8: 36.8°C
  - Wk 12: 36.9°C
  - Wk 16: 37.0°C
  - Wk 20: 36.4°C
  - Wk 26: 
  - Wk 38: 

- **Weight (Kg)**
  - Screen: 102.5 kg
  - SD1: 102.5 kg
  - SD8: 105.7 kg
  - SD22: 107.0 kg
  - Wk 8: 104.3 kg
  - Wk 12: 103.4 kg
  - Wk 16: 
  - Wk 20: 
  - Wk 26: 
  - Wk 38: 

#### Drug Exposure

- **Dosing**
  - Dummy Administrations are displayed using Number of Days since First Dose
  - List of distinct dummy doses administered to the overall population:
    - 0.26 (mL)
    - 0.60 (mL)
    - 0.75 (mL)
    - 1.50 (mL)
    - 7.60 (mL)

- **Screen:**
  - SD1
  - SD8
  - SD22
  - Wk 8
  - Wk 12
  - Wk 16
  - Wk 20
  - Wk 26
  - Wk 38

**Vital Signs (1 unscheduled visit(s) not displayed, refer to the detailed PDF Patient Profile)**

- **Vital Signs are displayed using their corresponding Visit Code**

**Laboratory Parameters (no unscheduled visit)**

- **Haemoglobin**
  - Screen: 117
  - SD1: 119
  - SD8: 132
  - SD22: 113
  - Wk 8: 119
  - Wk 12: 119
  - Wk 16: 108
  - Wk 20: 122
  - Wk 26: 
  - Wk 38: 

- **White Blood Cell c [pl]**
  - Screen: 9.2
  - SD1: 10.9
  - SD8: 14.7
  - SD22: 12.5
  - Wk 8: 8.1
  - Wk 12: 9.1
  - Wk 16: 10.1
  - Wk 20: 11.78
  - Wk 26: 
  - Wk 38: 

Extremely useful for **medical review** but could be also provided for the **section 16.4**
Key points in ICH E3 referring to statistical outputs production

Narrative

Subject: 101004
Randomized Arm: NIC .15
Investigator: 101A
Drug and Dose at Event Onset: 30 mg/h of NIC .15

Serious Adverse Event (coded term [reported term]): COMA [COMA]

Subject 101004 was a 48-year-old white female. Her medical history included focal deficit (1988), headache (1988), loss of consciousness (1988), vomiting (1988), other medical condition (1977) and allergies (start date unknown). She began dosing with 30 mg/h of nic .15 on 28 JAN 1988 (Day 1). The subject discontinued the trial on 31 JAN 1988 (Day 4) due to death.

On 28 JAN 1988 [Day 1] the subject experienced a coma (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. At the time of the event, the subject was taking 30 mg/h of nic .15 and had been at this dose for 1 day. The SAE occurred on the first day of dosing with any study medication. Trial medication had an action of drug withdrawn as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a ±3-day window of the onset of the SAE included brain oedema (mild), hydrocephalus (severe), hyperglycaemia (mild), hypotension (severe), intracranial pressure increased (severe), subarachnoid haemorrhage (severe) and vasoconstriction (severe). Concomitant medications taken at the onset of the SAE included docusate sodium (stool softener), phenobarbital (sedative), potassium supplements (fluids) and ranitidine (decrease acidity).

The subject had the following abnormal lab tests at baseline: high creatine kinase [411 U/L, range = (15 - 185)], high chloride [112 mmol/L, range = (97 - 107)], high leucocytes [21 U/L, range = (3 - 20)], low partial pressure carbon dioxide [239 Pa, range = (4655 - 5985)] and high partial pressure oxygen [31654 Pa, range = (9975 - 13965)]. The subject had no on-study lab tests with results different than baseline on or prior to the start day of the event. On the closest lab test day subsequent to the start of the event, the subject had the following on-study lab tests with results different than baseline: low blood urea nitrogen [2.142 mmol/L, range = (2.499 - 7.497), BL = normal], low carbon dioxide [91.065 mg/dL, range = (100.044 - 130.44), BL = normal], low creatinine [0.053040001768 mmol/L, range = (0.05746 - 0.10608), BL = normal] and normal leucocytes [11 U/L, range = (3 - 20), BL = high].

The investigator considered the AE to be related to study medication. The final outcome of the event was reported as recovered/resolved on 31 JAN 1988 (Day 4).

Generated with JMP® Clinical
Developing a Complete Picture of Patient Safety in Clinical Trials. RC Zink. RD Wolfinger. SESUG 2012

Usually written by the MW, but automation can be implemented especially for big trials
Key points in ICH E3 referring to statistical outputs production
As per FDA Portable Document Format (PDF) Specifications – Style Requirements

- **US Letter**
  - **Margins** as recommended by FDA PDF Specification. In general settings of 1 inch on each side of the page should be also enough to allow printing on A4 as well

- **Font sizes ranging from 9 to 12 points**
  - Times New Roman 12-point font is recommended for narrative text
  - For tables generally, **point sizes 9-10** are recommended for tables; smaller point sizes should be avoided. Ten point fonts are recommended for footnotes.
Key points in ICH E3 referring to statistical outputs production
SAS options/statements for controlling paper size and styles

**Paper Size, Orientation and Margins with SAS options**

```
option papersize="LETTER" orientation=LANDSCAPE
            topmargin="1in" bottommargin="1in" leftmargin="1in" rightmargin="1in";
```

**Setting fonts and size by modifying a template**

```
proc template;
   define style MyStyle / store=library.styles;
       parent = styles.sasdocPrinter;
   replace fonts /
       'TitleFont2' = ("Courier New",9pt)
       'TitleFont'  = ("Courier New",9pt)
   ;
```

Zoom, Zoom: Get your document to scale on all paper size. D. O’Connor. SAS Global Forum 2010
Key points in ICH E3 referring to statistical outputs production
SAS options/statements for controlling paper size and styles

**ODS Options e.g. the ‘page x of y’ dilemma**

```sas
ods escapechar="^";
title1 j=1 "Study Drug: MyDrug"
    j=r ' Page ^{thispage} of ^{lastpage}';
ods pdf file="MyFile.pdf" style=MyStyle;
/*Other SAS Statements*/
ods pdf close;
```

It controls special sequence for **in-line formatting**
(e.g. PDF, RTF, HTML)

The Greatest Hits: ODS Essentials Every User Should Know. C. Zender. NESUG 2011
Advanced RTF Layout with SAS. K. Glab. PhUSE 2007
Key points in ICH E3 referring to statistical outputs production
SAS options/statements for controlling paper size and styles

Other ad-hoc style setting within a SAS procedure
e.g. PROC REPORT

```sas
define text/display style(column)=
{just=left asis=on cellwidth=8.5 cm}
style(header)={just=left asis=on} flow id "Parameter";
```

Proc REPORT Tutorial. C. Zender. WUSS 2010
Key points in ICH E3 referring to statistical outputs production
As per FDA Portable Document Format (PDF) Specifications – Style Requirements

- Black is the recommended font color. Any colors used should be tested prior to submission by printing sample pages from the document using a grayscale printer
- Additional rules as per eCTD guidance concerning
  - File size
  - File name (e.g. avoid punctuation, underscore, spaces, etc.)
Key points in ICH E3 referring to statistical outputs production

Structure / Titles / Numbering for section 14 and 16.x

- Standard sections contents/numbering is proposed
- A hierarchical structure
  - Output titles and sub-titles, and their associated bookmarks are limited to 4 levels as per eCTD guidance.

For example for section 14

14.1 DEMOGRAPHICS DATA
14.2 EFFICACY DATA
14.3 SAFETY DATA
  14.3.1 Displays of Adverse Events
  14.3.2 Listings of deaths, other SAE and Significant AEs
  14.3.3 Narrative Deaths, Other serious......
  14.3.4 Abnormal Laboratory Value Listing (Each patient)
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ICH E3 Additional Considerations

Still space for interpretation / individual preferences e.g. medical writer

- Duplication of outputs in section 14 and in-text
- 16.4 for all trials, 16.4 and Subjects Profiles, 16.4 and SDTM
- Duplication of outputs (listings) in section 14 and 16.x, 16.2 and 16.4
- Exposure in section 14.3
- Concomitant Medications in section 14.1 or 14.3
ICH E3 Additional Considerations

Some recommendations – We must do it!

- Follow the eCTD and FDA PDF Specifications
  - Paper format including margins setting
  - Font style and size
  - Avoid use of coulors

- Adhere to key items in E3 structure
  - 14.1 for all demographics / data generated prior to experimental drug expose
  - 14.2 for efficacy
  - 14.3 for safety including any ‘interventions’ (e.g. exposure)
  - 16.X at least listings explicetely mentioned in the ICH E3

Out of scope of the presentation «non clinical» domains e.g. PK
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Technical Solutions

Software requirements overview

- Combine descriptive statistics including p-values for inferential tests
- Generates totals and subtotals within specified groups
- Full control of the denominator for percentage calculations
- Automatic rounding, formatting, and decimal point alignment of results
- Manages page changing based on user-defined groupings
- Headings span (multiple columns)
- Titles and footnote management
- Places information from a single record on multiple output lines
- Full control of titles and footnotes
- Allow creation of styled RTF tables for immediate use in Publishing software (e.g. WORD)
- Table of Contents Generation
- Management of template/standard libraries
Technical Solutions

Software requirements overview

- **SAS**
  - Procedures for output reporting e.g. TABULATE, REPORT, etc.
  - Procedures for statistical techniques/methods e.g. LIFETEST, GLM, etc.
  - ODS, Proc TEMPLATE, Proc DOCUMENT
  - Macro
    - No end-user application, No `proc CSR` or `proc TLF` yet

- **R**
  - Existing library for «R for Clinical Trial Reporting» FE Harrel (2007)
Technical Solutions

Software requirements overview

Others

- Pharmastat APT Analysis Library Tool for Clinical Trials Report Creation
- Dataceutics SAS/IntrNet based platform for Clinical Reporting
- ClinPlus
- SAS JMP Clinical

- SAS Drug and Device Development and other SAS tools for Life Science
- EntimICE
- Oracle Life Science

Still a bit away from the *push_the_bottom_away* theory
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Technical Solutions

In-house solutions (Sponsor)

Often each organization has its own tools/macro library/process

GBSOS - A Guidance for statistical outputs

5 GENERAL SPECIFICATIONS RELATED TO ALL OUTPUTS

5.3 Output is centered on the page

5.2 & 5.3 Titles left aligned

5.3 Text variables: column header and content left justified

5.4 Footnotes left aligned in this order including Source line 5.5 and output id 5.6

5.3 Numeric variables: column headers and content centered

5.3 Alignment on the decimal point

5.9 Data labels/formats match CRF/database
Technical Solutions

In-house solutions (Sponsor)

Additional rules / **policy** for outputs numbering

14.1 Demographics
14.2 Efficacy
14.3 Safety
14.3.0 Extent of exposure*
14.3.1 Adverse events
14.3.2 Listing of deaths, SAEs, etc
14.3.3 Case narratives
14.3.4 Listing of abnormal lab values
14.3.5 Lab tables*
14.3.6 Other tables*
14.4 PK*
14.5 PD*
14.6 Other data*

16.1.7 Randomization and Codes
16.1.9 Documentation of statistical methods
16.2.1 Discontinued subjects
16.2.2 Protocol deviations
16.2.3 Subj. excl. from efficacy analyses
16.2.4 Demographics
16.2.5 Compliance / drug conc. Data
16.2.6 Efficacy
16.2.7 Adverse events
16.2.8 Lab

* Sponsor addition

16.1.6 Listings of patients receiving test drug(s)/investigational product from specific batches, where more than one batch was use

16.1.9 (out of scope) SAP or description of key stats items

Technical Solutions

In-house solutions (Sponsor)

**SDOT** - A set of SAS macro to cover **standard** outputs

- **TABS**: Continuous / Categorical Standard Analysis Outputs
- **AE**: Adverse Events and Concomitant Medications
- **PDF**: Ad-hoc outputs
- **LST2PS**: PDF output production with hierarchical bookmarks

→ Started with excel outputs
→ Tried word outputs

→ **PDF** preferable solution for section 14 and 16.x

→ Standard SAS .LST file read and transformed to PS rendered to PDF
  + More stable
  + Size of output file
  - Less space available (monospace font)
  - Less styling options

→ .MHTM file
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Technical Solutions
Facilitate the work of the medical writer

- Provide section 14 and 16.x in PDF format with **bookmarks** to facilitate the production of the final CSR

Clinical Study Report - In-text tables, Tables Figures and Graphs, Patient and Individual Patient Data Listings: ICH E3 technical requisites and possible solution in SAS – A. Tinazzi – Seminario BIAS – Milano 22/02/2013
Technical Solutions
Facilitate the work of the medical writer
PDF Bookmark creation – In house solution (Sponsor)

Before

- Outputs where either generated in .XLS or RTF
- Rendered to PDF
- Bookmarks where created manually by the MW
Technical Solutions
Facilitate the work of the medical writer
PDF Bookmark creation – In house solution (Sponsor)

In-house solution (SAS macro)

- Standard SAS .LST output
- Rules for hierarchical titles
- .LST rendered to PDF and hierarchical titles captured from the .LST
- Postscript file with built-in bookmark from hierarchical titles automatically rendered to PDF
Technical Solutions

Facilitate the work of the medical writer
PDF Bookmark creation – In house solution (Sponsor)

In-house solution (SAS macro)

- **LST Rules for pagesize and linesize**

<table>
<thead>
<tr>
<th>Layout Number</th>
<th>Regulatory Approved</th>
<th>Number of lines</th>
<th>Number of characters per line</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>46</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>52</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>46</td>
<td>128</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>52</td>
<td>128</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>52</td>
<td>135</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>58</td>
<td>135</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>52</td>
<td>144</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>58</td>
<td>144</td>
</tr>
</tbody>
</table>

- **Example of postscript statements to control bookmarks**

```
[/Count 3 /Title "Bookmarks root node" /Dest /First_Link /OUT pdfmark
[/Count 0 /Title "Link to page 1" /Dest /First_Link /OUT pdfmark
[/Count 1 /Title "Link to page 2" /Dest /Second_Link /OUT pdfmark
[/Count 1 /Title "Link to page 3" /Dest /Third_Link /OUT pdfmark
[/Count 0 /Title "Link to page 4" /Dest /Fourth_Link /OUT pdfmark
```

Technical Solutions
Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x

- Default PDF bookmarked file
- ODS PROCLABEL to control standard SAS proc label (bookmark level 1)
- Proc options to control bookmark level 2 e.g. CONTENTS= in PROC REPORT
  DESCRIPTION= in SAS/GRAPH procedures
  - Some procedures have more than 2 levels e.g. PROC GLM
- Control bookmarks through PROC TEMPLATE
- Full bookmarks control through PROC DOCUMENT
Technical Solutions
Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x - Example

Create a PDF file with 4 outputs with the following hierarchical bookmarks:

14.1 DEMOGRAPHICS DATA
14.1.2 Subject Accrual
   Table 14.1.2.1 ITT Population
   PROC FREQ

14.1.6 Demographics Characteristics
   Table 14.1.6.1 ITT Population
   Listing 14.1.6.1 Detailed Listing
   PROC TABULATE
   PROC REPORT

14.2 EFFICACY DATA
14.2.1 Primary Endpoint
   Table 14.2.1.1 ITT Population
   PROC LOGISTIC with ODS SELECT
**Technical Solutions**

Facilitate the work of the medical writer

PDF Bookmark creation – Possible solutions with SAS 9.x - Example

### The best result with ODS statements and PROC options

```sas
ods PDF file='MYFILE.pdf' style=MyStyle;
ods PROCLABEL='14.1 DEMOGRAPHICS DATA';
proc tabulate data=pts CONTENTS="14.1.6 Demographics Characteristics";
...
run;
ods PDF close;
```

- Other possible statements controlling bookmarks generation:
  - `PDFTOC=n`
- Control the nr. of level to be displayed (ODS option)
  - `NOPTITLE`
- Suppress standard proc title (ODS option)
  - `/CONTENTS='Label'`
- option of TABLES statement (proc FREQ)
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Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x - Examples

The best result with ODS statements and PROC options

- Bookmarks not controlled through title statement
- Hierarchy within PROC
  - e.g. PROC LOGISTIC

- Not easy to control although further improvements are possible with template control (PROC TEMPLATE)
Technical Solutions
Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

- **SAS prior to v 8**
  - PROC producing «DATA» and defining «STYLE» for only one type of output .LST

- **SAS v 8**
  - ODS introduced the concept of DATA and STYLE object as OUTPUT object
  - OUTPUT objects can be not stored
Technical Solutions
Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

SAS 9 introduced the concept of Document
- ODS Output Objects in raw form stored in an item store
- Stored as hierarchical files
- Transform report without rerunning the analysis or repeating the database query by modifying and replaying an item store
- Control the report structure
- Absolute control over Table of Contents (e.g. PDF bookmarks)
- ODS DOCUMENT, PROC DOCUMENT, ODSDOCUMENT WINDOW
Technical Solutions

Facilitate the work of the medical writer

PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

```
ODS DOCUMENT NAME=TLF(WRITE);
  <SAS Proc Statement generating outputs>
ODS DOCUMENT CLOSE;
proc document name=TLF;
  list / levels =all;
run;quit;
```

Listing of: \Work.Tlf\ 
Order by: Insertion 
Number of levels: All

<table>
<thead>
<tr>
<th>Obs</th>
<th>Path</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\Freq#1</td>
<td>Dir</td>
</tr>
<tr>
<td>2</td>
<td>\Freq#1\Table#1</td>
<td>Dir</td>
</tr>
<tr>
<td>3</td>
<td>\Freq#1\Table#1\CrossTabFreqs#1</td>
<td>Crosstab</td>
</tr>
<tr>
<td>4</td>
<td>\Tabulate#1</td>
<td>Dir</td>
</tr>
<tr>
<td>5</td>
<td>\Tabulate#1\Report#1</td>
<td>Dir</td>
</tr>
<tr>
<td>6</td>
<td>\Tabulate#1\Report#1\Table#1</td>
<td>Table</td>
</tr>
<tr>
<td>7</td>
<td>\Report#1</td>
<td>Dir</td>
</tr>
<tr>
<td>8</td>
<td>\Report#1\Report#1</td>
<td>Dir</td>
</tr>
<tr>
<td>9</td>
<td>\Report#1\Report#1\Report#1</td>
<td>Table</td>
</tr>
<tr>
<td>10</td>
<td>\Logistic#1</td>
<td>Dir</td>
</tr>
<tr>
<td>11</td>
<td>\Logistic#1\ParameterEstimates#1</td>
<td>Table</td>
</tr>
</tbody>
</table>

→ PROC FREQ Output
→ PROC TABULATE Output
→ PROC REPORT Output
→ PROC LOGISTIC Output
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Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

An interactive environment to modify the document
- Adding a node
- Modifying a node
- Rename a node
- Move a node
- Same actions for a table
Technical Solutions

Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

PDF recreated

```
ods pdf file="<my file>"
  style=MYSTYLE;
proc document name=TLF;
  replay;
run;
ods pdf close;
```
Technical Solutions

Facilitate the work of the medical writer

PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

The SAS code generated by the «Document Recorder» facility

```
proc document name=MyDoc.TLF(UPDATE);

/*Move outputs to correct section/level and change the title*/
SETLABEL Freq#1\Table1#1 '14.1.2 Subject Accrual';
DIR \Freq#1\Table1#1;
SETLABEL \CrossTabFreqs#1 'Table 14.1.2.1 Subject Accrual - ITT Population';
COPY \Tabulate#1\Report#1 TO \Freq#1\Report#1;
......

<continue>
```
Technical Solutions

Facilitate the work of the medical writer
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

The SAS code generated by the «Document Recorder» facility

/* Create the missing level 2 for section 14.2 */
DIR \Logistic#1;
MAKE \Sub14_2_1;
SETLABEL \Sub14_2_1 '14.2.1 Primary Endpoint';
COPY \ParameterEstimates#1 TO Sub14_2_1#1\ParameterEstimates#1;

......
quit;
# Technical Solutions

Facilitate the work of the medical writer

PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

<table>
<thead>
<tr>
<th>Operation</th>
<th>PROC DOCUMENT</th>
<th>Windows</th>
<th>UNIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Display the path of the current directory</td>
<td>dir</td>
<td>chdir</td>
<td>pwd</td>
</tr>
<tr>
<td>Change the current directory to <em>path</em></td>
<td>dir <em>path</em></td>
<td>chdir <em>path</em></td>
<td>cd <em>path</em></td>
</tr>
<tr>
<td>List the contents of the current directory or given path</td>
<td>list <em>&lt;path&gt;</em></td>
<td>dir <em>&lt;path&gt;</em></td>
<td>ls <em>&lt;path&gt;</em></td>
</tr>
<tr>
<td>Copy a path</td>
<td>copy a to b</td>
<td>copy a b</td>
<td>cp a b</td>
</tr>
<tr>
<td>Move a path</td>
<td>move a to b</td>
<td>move a b</td>
<td>mv a b</td>
</tr>
<tr>
<td>Create a new directory</td>
<td>make <em>path</em></td>
<td>mkdir <em>path</em></td>
<td>mkdir <em>path</em></td>
</tr>
<tr>
<td>Create a symbolic link</td>
<td>link a to b</td>
<td>N/A</td>
<td>ln –s a b</td>
</tr>
<tr>
<td>Create a hard link</td>
<td>link a to b / hard</td>
<td>N/A</td>
<td>ln a b</td>
</tr>
<tr>
<td>Rename a path</td>
<td>rename a to b</td>
<td>rename a b</td>
<td>mv a b</td>
</tr>
<tr>
<td>Delete a path</td>
<td>delete <em>path</em></td>
<td>del <em>path</em></td>
<td>rm <em>path</em></td>
</tr>
<tr>
<td>Current directory specifier</td>
<td>^</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Parent directory specifier</td>
<td>^^</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

ODS DOCUMENT from scratch. KD Smith SAS Global Forum 2012
## Technical Solutions

Facilitate the work of the medical writer

**PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept**

<table>
<thead>
<tr>
<th>Operation</th>
<th>Command</th>
</tr>
</thead>
<tbody>
<tr>
<td>List all documents in library</td>
<td>doc library=library</td>
</tr>
<tr>
<td>Open document for update</td>
<td>doc name=document</td>
</tr>
<tr>
<td>Close the current document</td>
<td>doc close</td>
</tr>
<tr>
<td>Delete document</td>
<td>delete document</td>
</tr>
<tr>
<td>Import a data set, grseg, or text file to path</td>
<td>import data</td>
</tr>
<tr>
<td>Create a new note at path</td>
<td>note path &quot;text&quot;</td>
</tr>
<tr>
<td>Set the label of path</td>
<td>setlabel path &quot;text&quot;</td>
</tr>
<tr>
<td>Set the nth line before the note of path</td>
<td>obbnote&lt;n&gt; path &quot;text&quot;</td>
</tr>
<tr>
<td>Set the nth line after the note of path</td>
<td>obanote&lt;n&gt; path &quot;text&quot;</td>
</tr>
<tr>
<td>Set the nth line of the title of path</td>
<td>obtitle&lt;n&gt; path &quot;text&quot;</td>
</tr>
<tr>
<td>Set the nth line of the subtitle of path</td>
<td>obstitle&lt;n&gt; path &quot;text&quot;</td>
</tr>
<tr>
<td>Set the nth line of the footnote of path</td>
<td>obfootn&lt;n&gt; path &quot;text&quot;</td>
</tr>
<tr>
<td>Control the page breaks of path</td>
<td>obpage path / &lt;after&gt; &lt;delete&gt;</td>
</tr>
<tr>
<td>Display the template code for path</td>
<td>obtempl path</td>
</tr>
<tr>
<td>Hide path from being replayed</td>
<td>hide path</td>
</tr>
<tr>
<td>Unhide path from being replayed</td>
<td>unhide path</td>
</tr>
</tbody>
</table>

ODS DOCUMENT from scratch. KD Smith SAS Global Forum 2012
Agenda

- Introduction to ICH E3
- Key points in ICH E3 referring to statistical outputs production
- ICH E3 Additional Considerations
- Technical Solutions
  - Software requirements overview
  - In-house solutions
  - Facilitate the work of the medical writer
  - Other possible topics for discussion
- References
Other possible topics for discussion related to statistical outputs production

- PhUSE/FDA Working Group (see Wiki Page for Development of Standard Scripts for Analysis and Programming)
- Layout examples in ADaM AE, TTE and ADaM examples in commonly used statistical analysis methods
- Analysis Results Metadata
- Traceability
- Validation / Quality Control
- Documentation / Procedures / Templates
- ADaM not covered but is should be considered as a statistical output
Agenda

- Introduction to ICH E3
- Key points in ICH E3 referring to statistical outputs production
- ICH E3 Additional Considerations
- Technical Solutions
  - Software requirements overview
  - In-house solutions
  - Facilitate the work of the medical writer
  - Other possible topics for discussion

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Questions

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