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STATISTICAL SOFTWARE & SERVICES

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**

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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 Techincal Document(eCTD)
  - FDA Portable Document Format (PDF) Specifications

Introduction to ICH E3

E3 Implemention Working Group Q&A 7 June 2012

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- It is a guidance not a set of rigid requirements or a **template**
- **Modifications** and **adaptions** 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

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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

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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 eficacy 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

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In-text tables

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

Subject Disposition - ITT Population
Output ID: T_DISPO1 06JAN2012 14:24

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

Sponsor SDOT Tool

- 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)

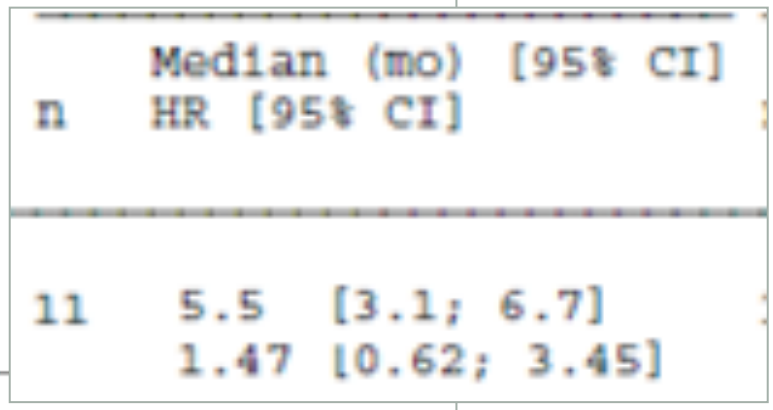
Key points in ICH E3 referring to statistical outputs production

Post-text tables

15.2.1 : Progression Free Survival Time
Table 15.2.1.2 : All Subgroups - ITT Population

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

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)



Sponsor SDOT Tool

Complex output summarizing information coming from different PROCs e.g. LIFETEST (Median 95%CI) and PHREG (HR 95%CI) to save space and improve readibility

Key points in ICH E3 referring to statistical outputs production

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Post-text listings

15.3.20 : Special Adverse Events
Listing 15.3.20.5 : Listing of Subjects with Haemorrages – S

Actual Treatment	Subject					
C	03012003	AE Preferred term : EPISTAXIS Symptoms as reported : EPISTAXIS Start : 02AUG2010 End : 18JAN2011	NCI-C MILD Outco recov Serio	ot	Relationship to Relationship to Relationship to	:RELATED :RELATED :RELATED
	03032001	AE Preferred term : EPISTAXIS Symptoms as reported : EPISTAXIS Start : 10APR2010 End : 16APR2010	NCI-C MILD Outco Recov Serio	ot resolved : N	Relationship to Relationship to	:RELATED :NOT RELATED
		AE Preferred term : LIP HAEMORRHAGE Symptoms as reported : BLEEDING ON LEVEL OF LIPS Start : 10APR2010 End : 16APR2010	NCI-C MILD Outco Recovered/resolved Serious AE : N	de : GRADE 1 OR	Relationship to Relationship to Relationship to	:RELATED :RELATED :NOT RELATED
		AE Preferred term : SPONTANEOUS HAEMATOMA Symptoms as reported : SPONTANEOUS HEMATOMAS ON HANDS Start : 02OCT2010 End : 26OCT2010	NCI-CTC-Grade : GRADE 1 OR MILD Outcome : Recovered/resolved Serious AE : N		Relationship to Relationship to Relationship to Relationship to Relationship to	:RELATED :RELATED :NOT RELATED :NOT RELATED :NOT RELATED
	03032006	AE Preferred term : HAEMATOMA Symptoms as reported : HEMATOMAS Start : 16JUN2011 End : 06JUL2011	NCI-CTC-Grade : GRADE 1 OR MILD Outcome : Recovered/resolved Serious AE : N		Relationship to Relationship to Relationship to Relationship to Relationship to	:NOT RELATED :NOT RELATED :NOT RELATED :NOT RELATED :NOT RELATED

Dictionary Coding: MedDRA version 14.0.

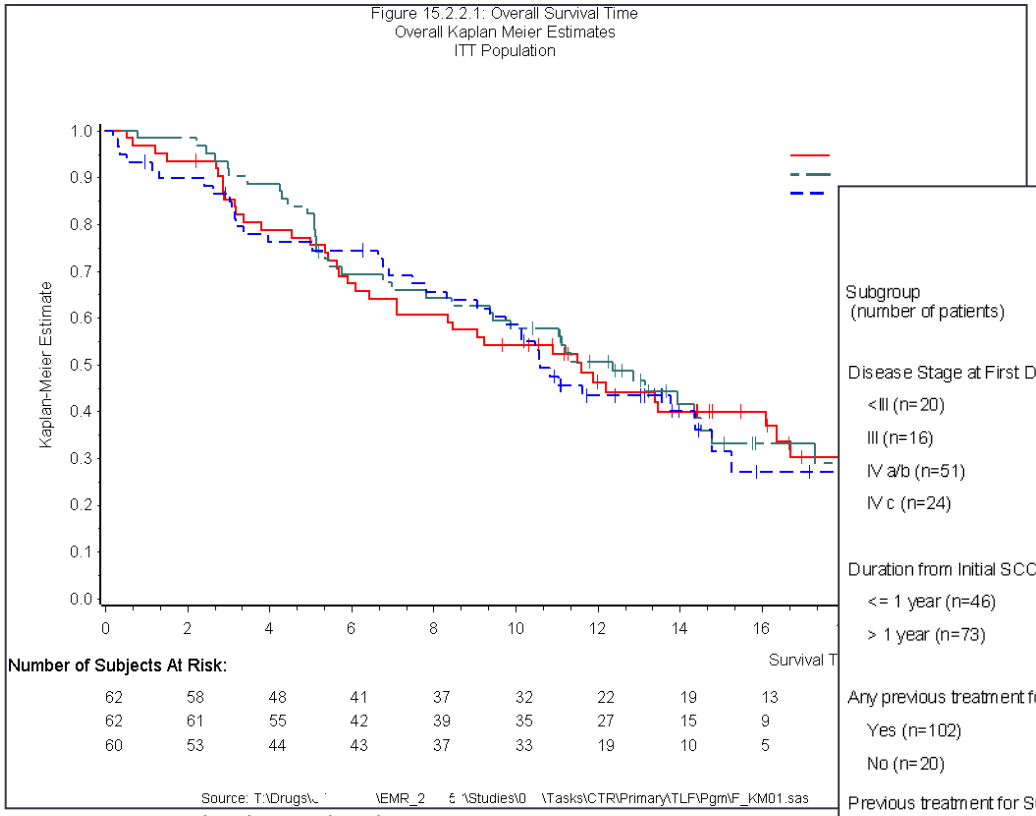
SAS Proc Report

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

Proc REPORT Tutorial. C. Zender. WUSS 2010
Beyond the Basic: Advanced REPORT Procedure Tips and Tricks Updated for SAS 9.2. A. McMahill Booth. SAS Global Forum 2011

Key points in ICH E3 referring to statistical outputs production

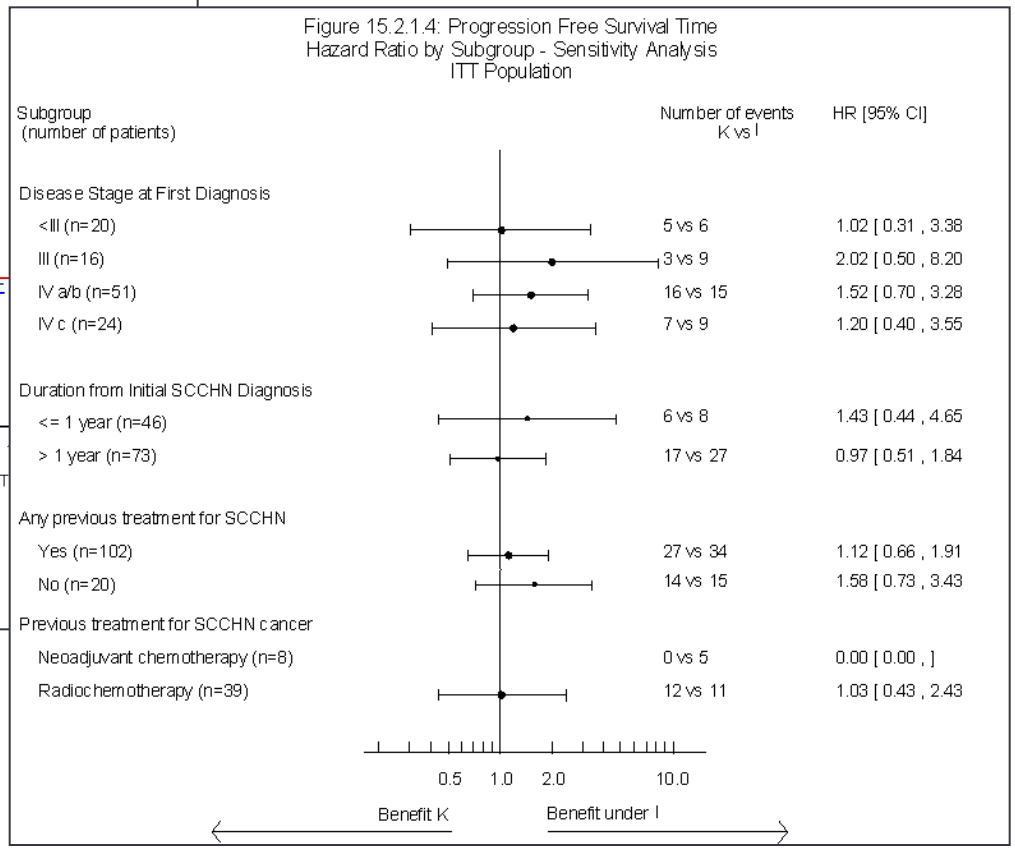
Figures



Sponsor Standard Graph Library

Should allow **B&W printing** without loosing any information. Their display should be verified

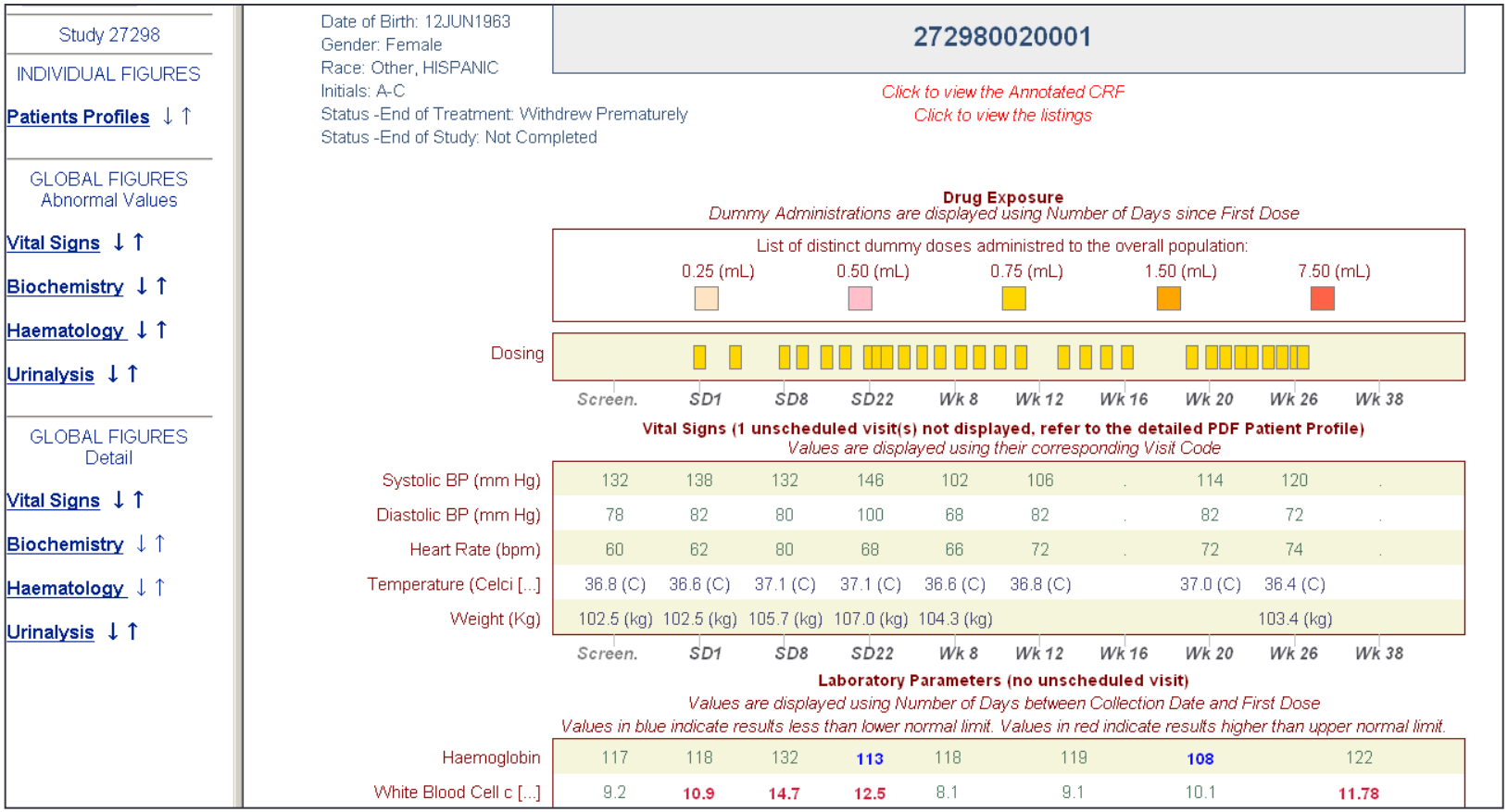
EMF, EPS, WMF and CGM are **reccomended** file formats



Sponsor Standard Graph Library

Key points in ICH E3 referring to statistical outputs production

Subject Profile



Sponsor Patient Profile Tool

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

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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 28JAN1988 (Day 1). The subject discontinued the trial on 31JAN1988 (Day 4) due to death.

On 28JAN1988 (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 softner), 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 - 195)], high chloride [112 mmol/L, range = (97 - 107)], high leukocytes [21 U/L, range = (3 - 20)], low partial pressure carbon dioxide [2394 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 [91.308 mg/dL, range = (100.004 - 130.44) , BL = normal], low creatinine [0.053040001768 mmol/L, range = (0.05746 - 0.10608) , BL = normal] and normal leukocytes [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 31JAN1988 (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" botttommargin="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

```
ods escapechar="^";
title1 j=l "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

```
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
Beyond the Basic: Advanced REPORT Procedure Tips and Tricks Updated for SAS 9.2. A. McMahill Booth. SAS Global Forum 2011

Key points in ICH E3 referring to statistical outputs production

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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 o 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

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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 reccomendations – 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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Techinical Solutions

Sofware 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

Techinical Solutions

Sofware 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)

Techinical Solutions

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Sofware requirements overview

Others

- Pharmastat APT Analysis Library Toold 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

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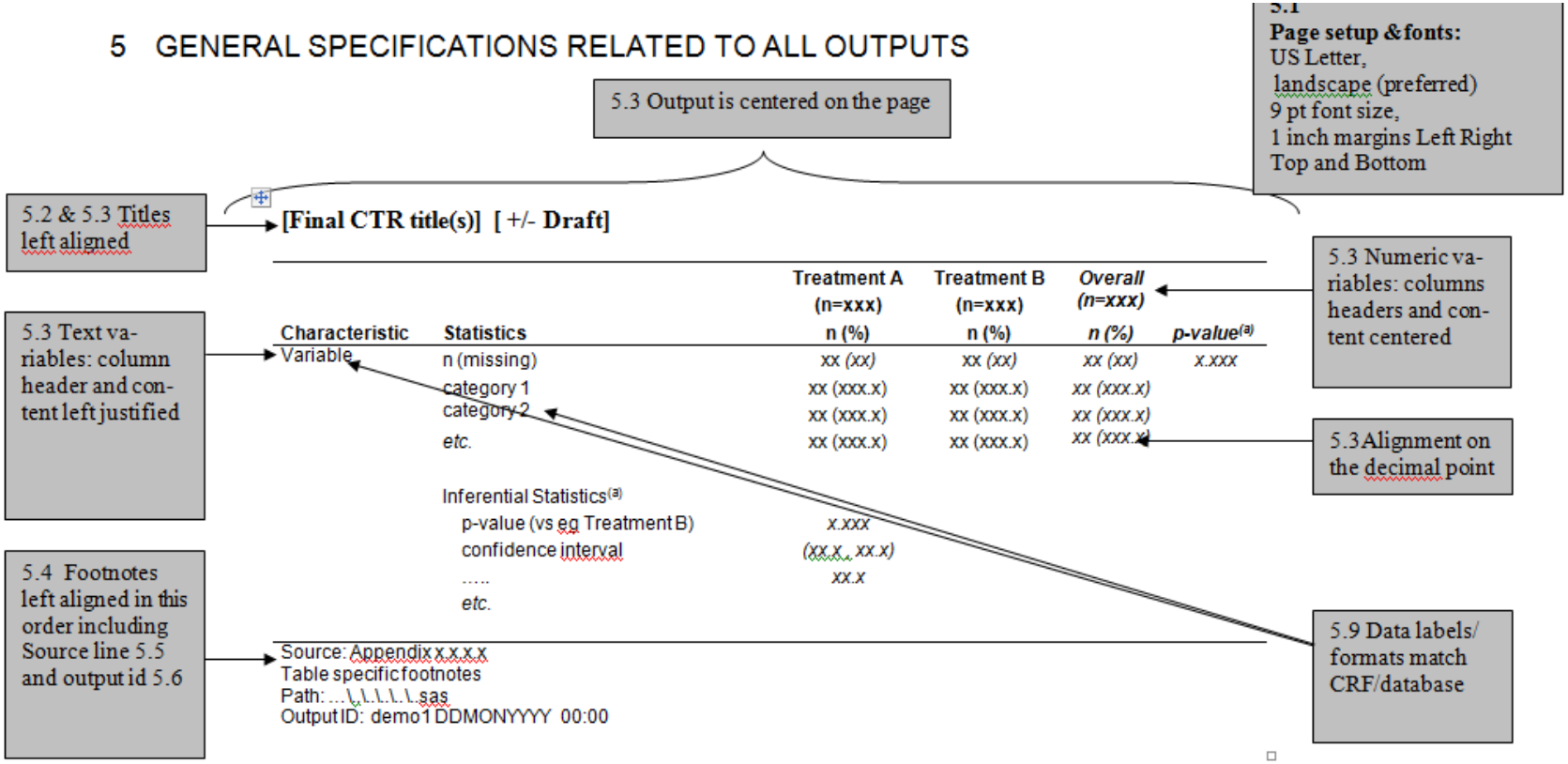
In-house solutions (Sponsor)

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

GBSOS - A Guidance for statistical outputs



Technical Solutions

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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*

* Sponsor addition

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

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

FDA http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4430b1-56%20S01-01US%20Statistical%20Analysis%20Plan.pdf

Technical Solutions

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In-house solutions (Sponsor)

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

- TABS: Continuos / 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
} .MHTM file

→**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

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Technical Solutions

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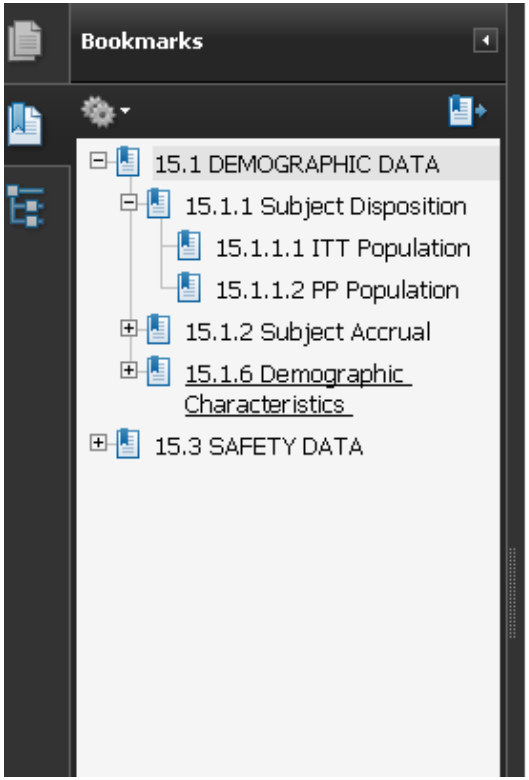
Facilitate the work of the medical writer

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



15.1 : DEMOGRAPHIC DATA
15.1.1 : Subject Disposition
Table 15.1.1.1 : ITT Population

Characteristic	Group A (N=36) N (%)	Group B (N=41) N (%)	Placebo (N=56) N (%)
All Screened Subjects			
Safety Population	33 (91.7)	36 (87.8)	50 (89.3)
ITT Population	33 (91.7)	37 (90.2)	51 (91.1)
Per Protocol Population	23 (63.9)	24 (58.5)	38 (67.9)
Total number (%) of discontinued subjects	31 (86.1)	36 (87.8)	50 (89.3)
Reason For Discontinuation As Randomized	31 (100.0)	36 (100.0)	50 (100.0)
Adverse Event	5 (16.1)	5 (13.9)	11 (22.0)
Death	6 (19.4)	2 (5.6)	5 (10.0)
Inclusion And/Or Exclusion Criteria Not Pullfilled	0 (0.0)	0 (0.0)	1 (2.0)
Subject Withdrew Consent	3 (9.7)	0 (0.0)	5 (10.0)
Progressive Disease	14 (45.2)	21 (58.3)	19 (38.0)
Symptomatic Deterioration	0 (0.0)	0 (0.0)	3 (6.0)
Others	3 (9.7)	8 (22.2)	6 (12.0)

Technical Solutions

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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

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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

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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

Layout Number	Regulatory Approved	Number of lines	Number of characters per line
1	Yes	46	120
2	Yes	52	120
3	Yes[1]	46	128
4	Yes[1]	52	128
5	No	52	135
6	No	58	135
7	No	52	144
8	No	58	144

- 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 5) /Dest /Fifth_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

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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 Characteristis

Table 14.1.6.1 ITT Population — PROC TABULATE

Listing 14.1.6.1 Detailed Listing — PROC REPORT

14.2 EFFICACY DATA

14.2.1 Primary Endpoint

Table 14.2.1.1 ITT Population — PROC LOGISTIC with ODS SELECT

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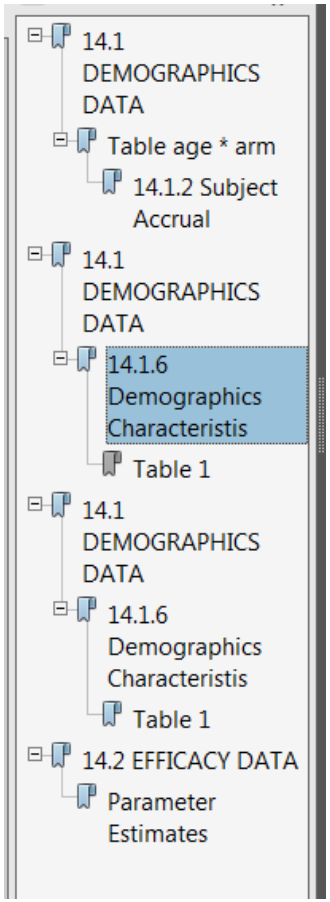
PDF Bookmark creation – Possible solutions with SAS 9.x - Example

The best result with ODS statements and PROC options




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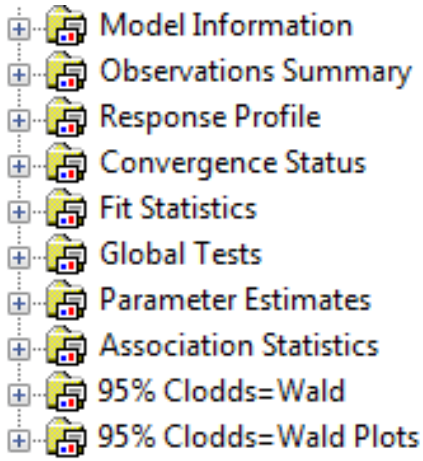
PDF Bookmark creation – Possible solutions with SAS 9.x - Examples

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)

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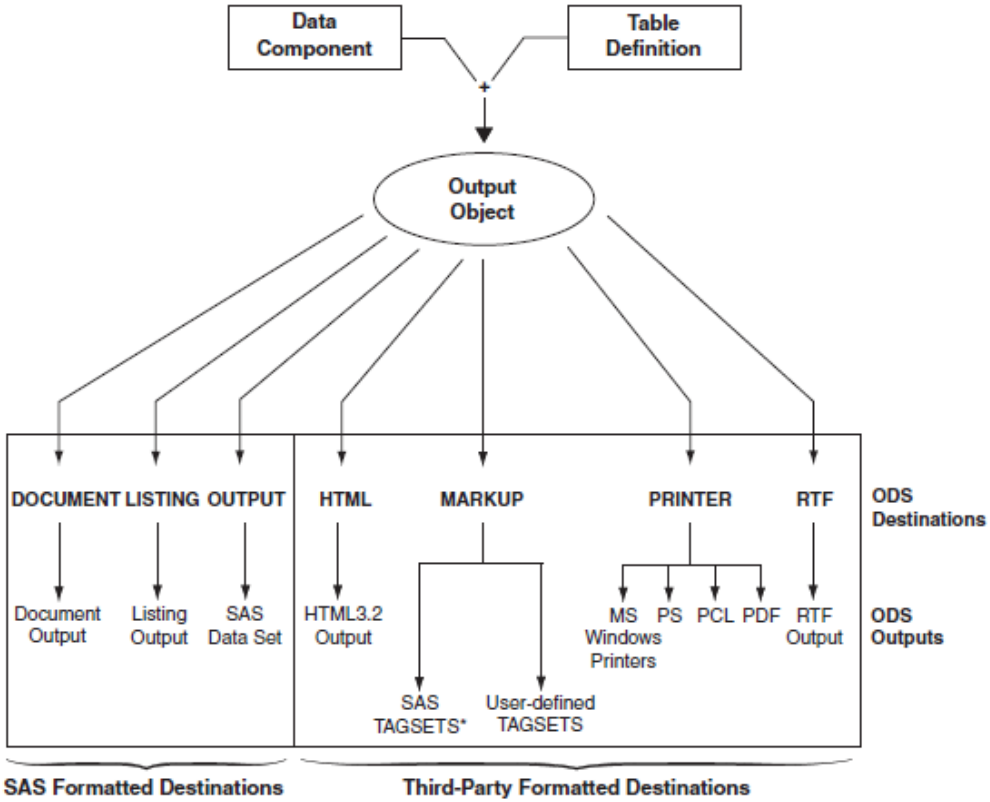
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept

- 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



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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

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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

  Obs    Path                                        Type
------------------------------------------------------------
    1  \Freq#1                                      Dir
    2  \Freq#1\Table1#1                             Dir
    3  \Freq#1\Table1#1\CrossTabFreqs#1             Crosstab
    4  \Tabulate#1                                  Dir
    5  \Tabulate#1\Report#1                         Dir
    6  \Tabulate#1\Report#1\Table#1                 Table
    7  \Report#1                                    Dir
    8  \Report#1\Report#1                           Dir
    9  \Report#1\Report#1\Report#1                  Table
   10  \Logistic#1                                  Dir
   11  \Logistic#1\ParameterEstimates#1             Table
```

→ PROC FREQ Output

→ PROC TABULATE Output

→ PROC REPORT Output

→ PROC LOGISTIC Output

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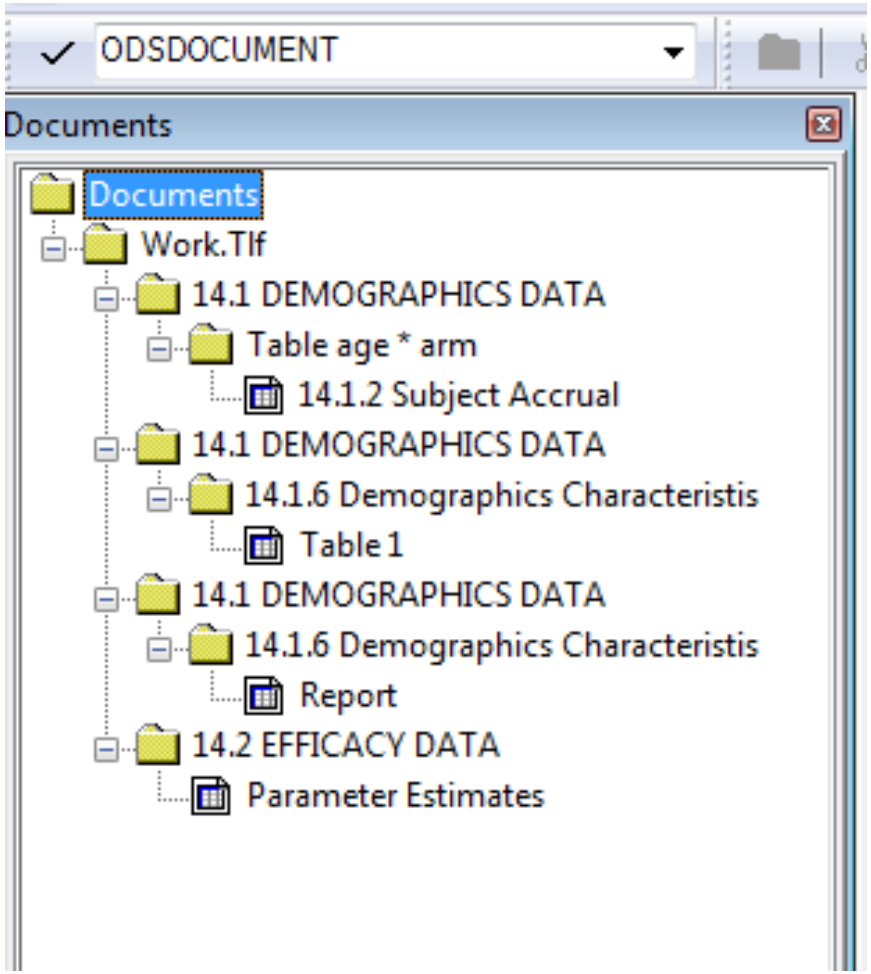
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept



An interactive environment to modify the document

- Adding a node
- Modifying a node
- Rename a node
- Move a node
- Same actions for a table

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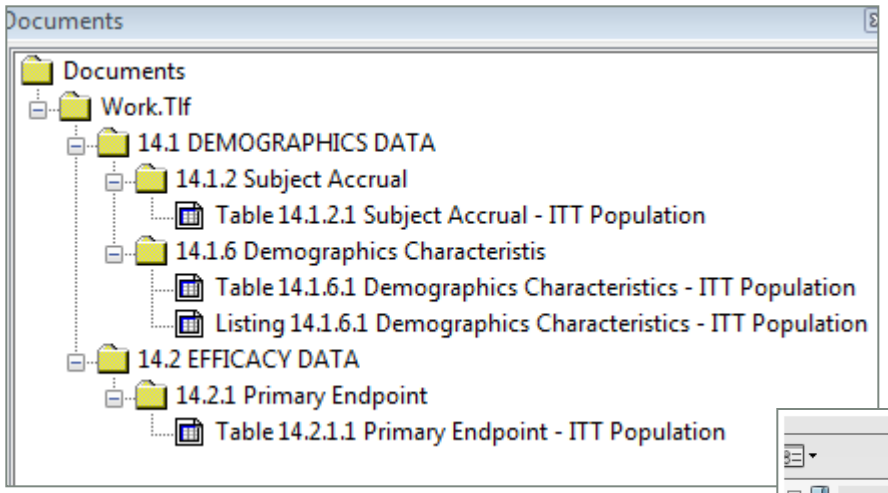
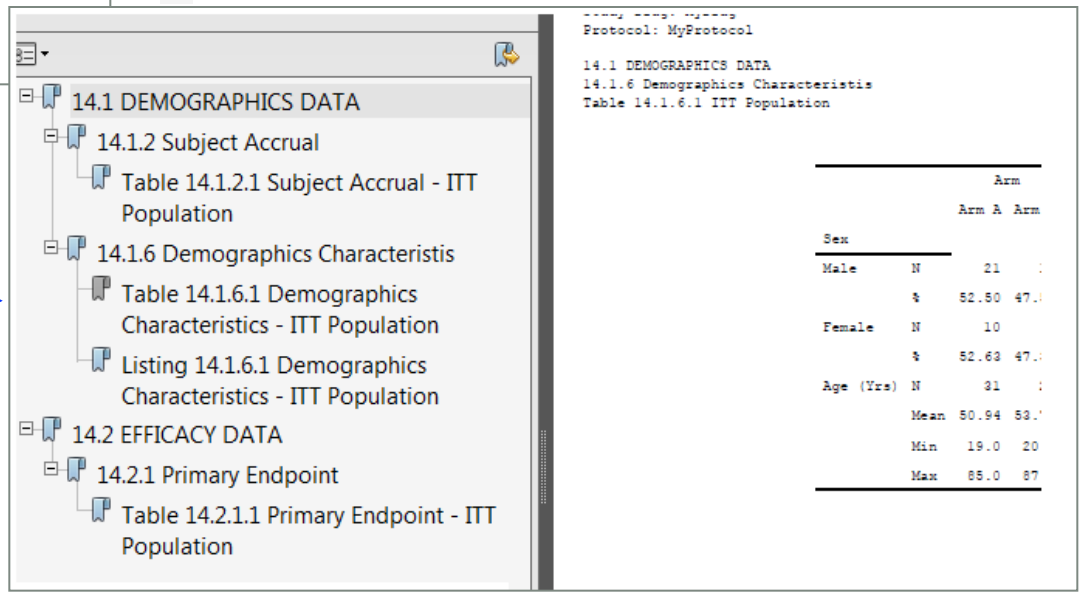
PDF Bookmark creation – Possible solutions with SAS 9.x – The new DOCUMENT concept



Document modified with ODSDOCUMENT point and click tool

PDF recreated

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



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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>

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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;
```

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

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

ODS DOCUMENT from scratch. KD Smith SAS Global Forum 2012

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

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

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

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- 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 statitical output

Agenda

- Introduction to ICH E3
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- Technical Solutions
  - Software requirements overview
  - In-house solutions
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  - Other possible topics for discussion
- **References**

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Questions

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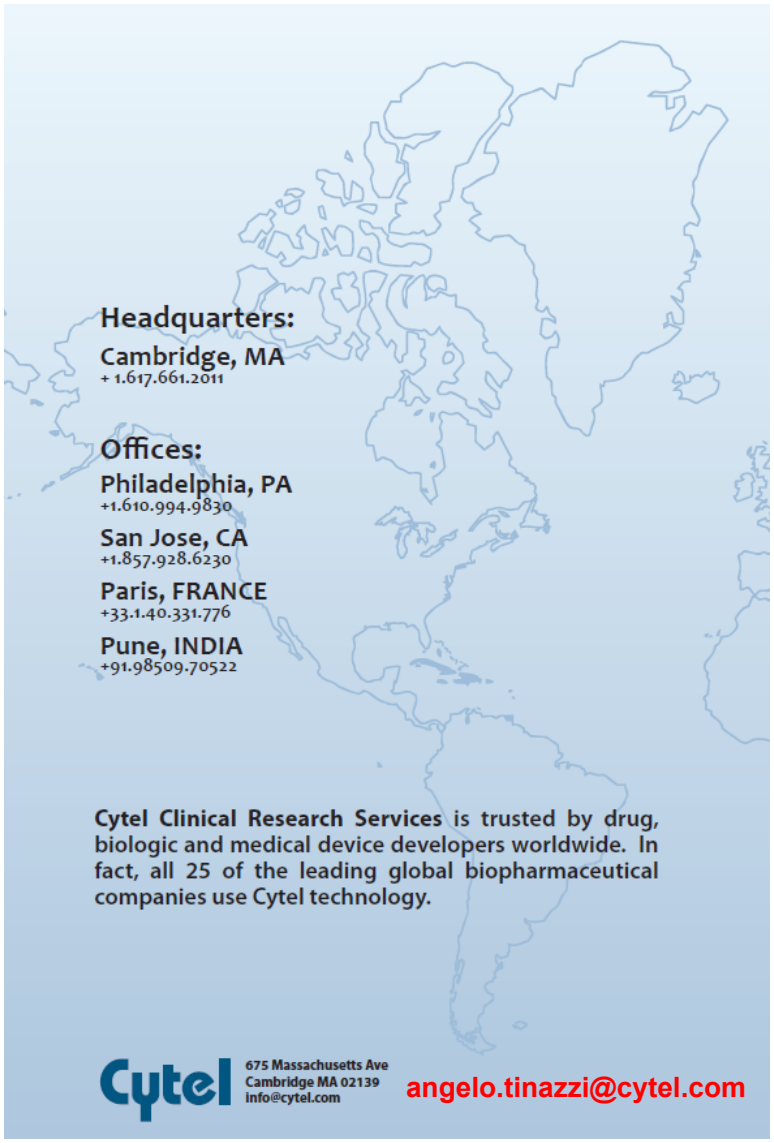

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