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Displaying the ODM-XML as a CRF Rendition Using a Style Sheet

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Meet the Speaker

Jørgen Mangor Iversen

Title: Clinical Standards Developer

Organization: LEO Pharma A/S

Jørgen has been programming for more than 40 years in many industries, the last 17 years in pharma, implementing CDISC standards. He has continuously educated himself in computer science in parallel to full time work and holds a B.Sc. in Computer Science and a Master of IT in Software Construction. In all his work, metadata and standards has always been a key focus point, acknowledging that standards makes programming easier, not harder. The last 4 years Jørgen has devoted all his time to developing metadata, as well as standards and tools for metadata



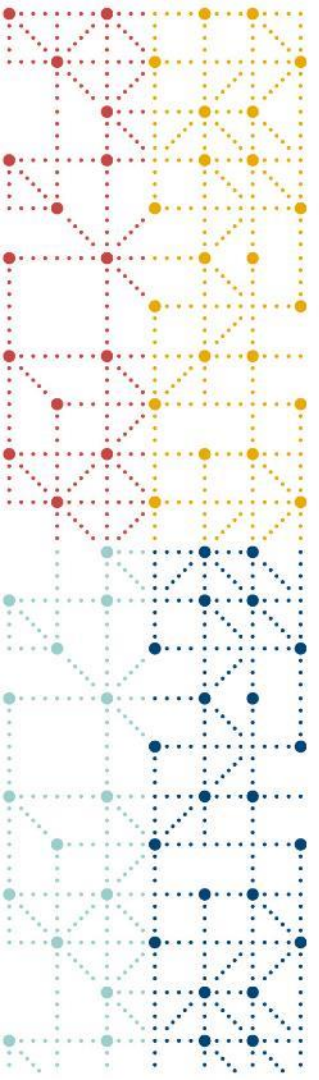
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- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *The author owns shares in these companies*
 - *LEO Pharma A/S*
 - *Nimbus Motorcycles*



Agenda

1. Problem and rationale
2. Displaying XML files with style sheets
3. ODM-XML
4. Creating PDF version of ODM-XML
5. Interlinking ODM-XML and Define documents



Problem and rationale

Identified issues with the creation of SDTM annotations to CRF forms and collection of references for define documents

Sample Forms visualizations

- Yellow boxes here show OIDs in place of SDTM variables
- Location of yellow boxes are difficult to control
- Yellow boxes overlay CRF text
- Larger yellow boxes (rich SDTM annotations) leads to clutter
- Manual process to rearrange yellow boxes

Sample form showing annotations distant from data collection fields

37 Subject identification		g.dm2
1.1	Subject identification number i.subject2 bject ID) (Transferred from IRT)	
1.2	Site identification number i.siteid Transferred from IRT)	

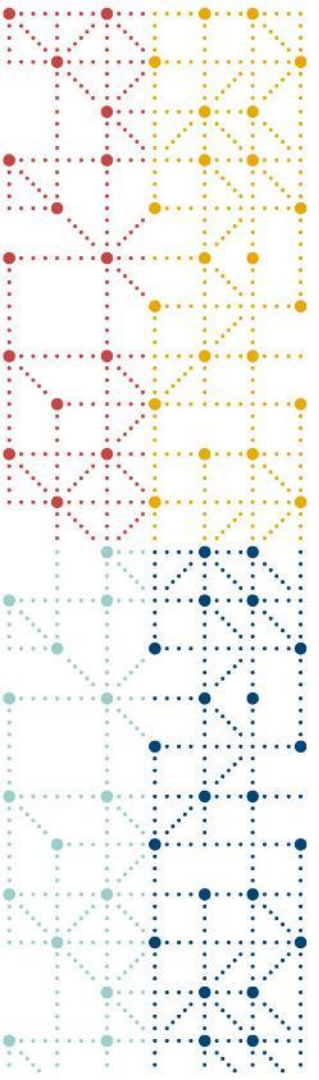
Sample form showing annotations overlapping CRF text

45 Visit		f.sv g.sv
1.1	Visit date # i.svstdat D-MMM-YYYY)	
2.1	Visit type 1.0249.LP0133	<input type="radio"/> Site visit <input type="radio"/> Phone vi CL.0067.LEOCT <input type="radio"/> Covid pandemic <input type="radio"/> Other CL.0088.1426
2.2	If Phone visit, ISpecify why 1.0312.1426 ccur?	
2.3	If Other, ISpecify 1.0313.1426	
Form Design Notes The form is called Visit type in Veeva		
Question Design Notes		
Visit date	In Veeva the visit date is not a part of a form. If a visit is not done the Did not occur field will have to be used. If ticked 'subject missed event' a comment must be made in the comment log for why the subject missed the event.	

Collection of page references

Define document related issues

- Traditionally, page references uses the page numbers of the CRF forms as origins in define-xml
- Collection of page numbers is usually a manual process (labor intensive)
- Page numbers only makes sense on paper, not in searchable electronic documents (xml, pdf)
- Page numbers are inherently study specific
 - Define origins needs to change for the same form from study to study, as page numbers change with different form collections and visit schedules
 - Page number add little value to electronic documents with clickable navigation
 - Page numbers prevent standardization and reuse of define metadata (origin)
 - Printed page numbers in pdf documents are rarely aligned with physical page numbers, leading to confusion



Displaying XML files with style sheets

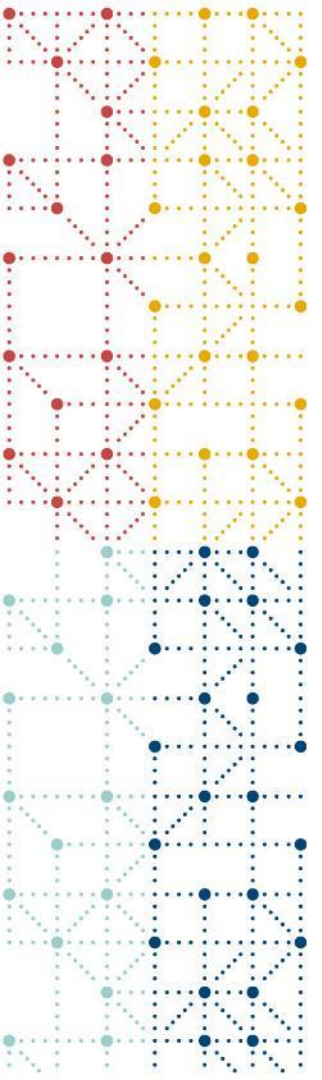
Well established technology



Displaying XML files with style sheets

Rationale for using a style sheet for odm-xml

- Define.xml has imbedded link to style sheet **define2-0-0.xsl**
 - Modern browser ignores imbedded style sheets
 - Internet Explorer displays correct but is deprecated
- New concept for ODM-XML
 - Parallel to define.xml
- XSLT version 1.0 imbedded in browsers via JavaScript
 - Chrome, Edge, Firefox, Internet Explorer
- External XML style sheets engines
 - SAS **proc xsl** and **saxon** supports XSLT version 2.0
 - PowerShell supports versions 1.0, 2.0, 3.0
 - Gnome xsltproc supports version 1.0



ODM-XML

Sample CRF elements created by applying the style sheet to odm-xml

Study example

Front page and visit matrix

- Study
- Name
- Additional information
- Protocol
- Date and time
- Company name
- Logo
- Visit matrix
 - Every form name is a link
 - Every visit name is a link

Study

CRF Specification for 1426

SDTM IG 3.2.1, ADaM IG 1.1, NCI CT 2021-09-24, MedDRA version 24.0, May 2021, WHO Drug March 2021

Protocol Name: LP0333-1426

Creation date: 2022-08-30 time:

LEO Pharma A/S



Visit Matrix

Event/ Form	Visit 1/Screening	Visit 2/Week 0	Visit 3/Week 2	Visit 4/Week 4	Visit 5/Week 8	Visit 6/Week 12	Visit 7/Week 16	Early Termination Visit	Follow-up visit	Primary endpoint visit	AE/CNCP/Other events involving IMP	Unscheduled visit	Trial Completion/Discontinuation	Patient Supply and Accountability Log	Comments Log
Subject identification	✓														
Visit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Informed consents adolescent	✓														
Informed re-consent adolescent	✓														
Demographics	✓														
Rescreen	✓														
Subject eligibility	✓	✓													
Fitzpatrick skin type	✓														
Medical and surgical history	✓														

Study example

Forms with notes and SDTM annotations

- SDTM annotations in a separate column
- LEO Notes can be removed via button
- Form notes indicated by #
- Question notes indicated by #
- Notes reference questions via numbers
 - Section OrderNumber.(dot) Question OrderNumber
- Buttons are non-printable

Subject Identification

LEO Note: This form can be named Subject identification number if needed. This form is a default form in RAVE.

Ref	CRF Question	Data Collected	SDTM Annotations
1.1	Subject identification number (subject ID) (Transferred from IRT) LEO Note: This item is a system subject identifier created by the DM system. Sometimes it is called CRF Number or subject number. This item can also be collected on other forms or on all forms in the header of the CRF. Please follow LEO syntax for defining the subject identification number.	<input type="text"/> Text	DM.SUBJID
1.2	Site identification number (Transferred from IRT) LEO Note: Please follow LEO syntax for defining the site identification number.	<input type="text"/> Text	DM.SITEID

Visit

Ref	CRF Question	Data Collected	SDTM Annotations
1.1 #	Visit date	<input type="text"/> DD-MMM-YYYY Date Always collect dates as DD-MMM-YYYY and store dates as ISO8601 in SDTM.	SV.SVSTDTCC
2.1	Visit type	<input type="radio"/> Site visit (SITE VISIT) <input type="radio"/> Phone visit (PHONE VISIT)	CO.COVAL, Use CO COREF to indicate which visit, by entering visit name into CO COREF. Use the same visit name as used for TV.VISIT
2.2	[If Phone visit,]Specify why the site visit did not occur?	<input type="radio"/> Covid pandemic (COVID PANDEMIC) <input type="radio"/> Other (OTHER)	CO.COVAL, Prefix CO.COVAL with "REASON SITE VISIT DID NOT OCCUR." Use CO COREF to indicate which visit, by entering visit name into CO COREF. Use the same visit name as used for TV.VISIT
2.3	[If Other,]Specify	<input type="text"/> Text	CO.COVAL, Prefix CO.COVAL with "OTHER REASON SITE VISIT DID NOT OCCUR." Use CO COREF to indicate which visit, by entering visit name into CO COREF. Use the same visit name as used for TV.VISIT

Form design note

The form is called 'Visit type in Veeva'

Question design note(s)

Question	Note
1.1	"In Veeva the visit date is not a part of a form. If a visit is not done the Did not occur field will have to be used. If ticked 'subject missed event' a comment must be made in the comment log for why the subject missed the event."

LEO notes Off and On | Scroll to the top

Standard example

Title and table of contents

- Standard/Study title from ODM
 - `<Study OID="STD_X" Of
OID="SDY_Y">`
- Version number from file name
- Status from file name
- No visit matrix

Standard

CRF Specification for LEO Common

Version 20

Status: Draft

LEO Common

Creation date: 2022-12-19 time:

LEO Pharma A/S



Table of Contents

<Type of skin biopsy>

<Type of skin biopsy>

<Validated investigator global assessment for atopic dermatitis (viGA-AD) or investigator's global assessment for chronic hand eczema (IGA-CHE)>

Adverse event

AE/CM/CP<events /Other event involving IMP>

Age

Atopy history

Blood biomarkers

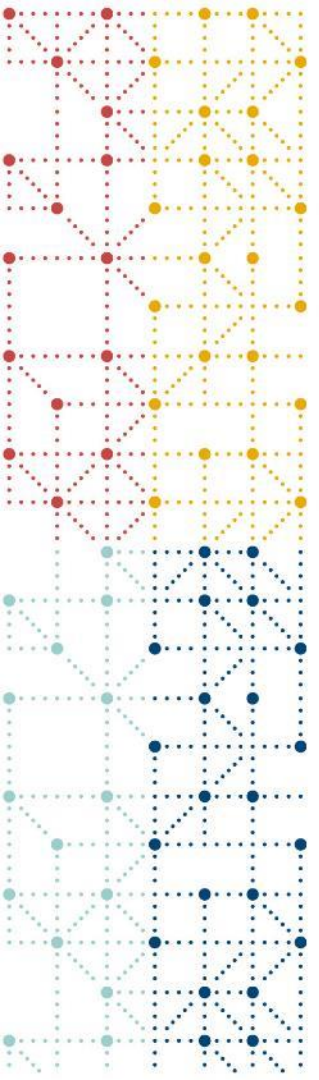
Body measurements

Body surface area involvement

Central laboratory

Comments log

[LEO notes Off and On](#) [Scroll to the top](#)



Creating PDF version of ODM-XML

Leave all formatting to the browser

Creating PDF version of ODM-XML

Proposed solution using a web page

- Freely available on GitHub in a PHP version
 - Upload as temporary and never retained
- Information extracted from file name
- Style sheet name controls options
- Selection of document types
 - Specification: maximum information
 - SDTM annotated CRF (acrf)
 - Blank CRF (bcrf)
 - Book: CRF pages per visit
- Optional company name on front page
- Optional company logo on front page

Display ODM-xml or Define-xml files in the browser

Usage

Choose a valid XML document and display it in the browser using the appropriate style sheet. Style sheet must exist in the same folder as the XML file. Please allow up to 20 seconds for a large XML file to render. Add an optional company name and an optional image file of the company logo to be part of the generated CRF pages.

Selection

XML file: No file chosen

Naming template:

XSL Style Sheet: No file chosen

Parameters for the CRF

ODM-XML display type: SDTM annotated CRF specification Display CDASH annotations
 SDTM annotated CRF (acrf)
 Blank CRF (bcrf)
 CRF book (forms per visit)

Company Name:

Company Logo (image file): No file chosen

Parameters for Define-xml v 2

Number of CodeListItems to display: 0 = No CodeListItems, 999 = All CodeListItems

Display Methods table:

Display Comments table:

Display Prefixes ([Comment], [Method], [Origin]):

Display Length, Display Format and Significant Digits:

Display

Creating PDF documents

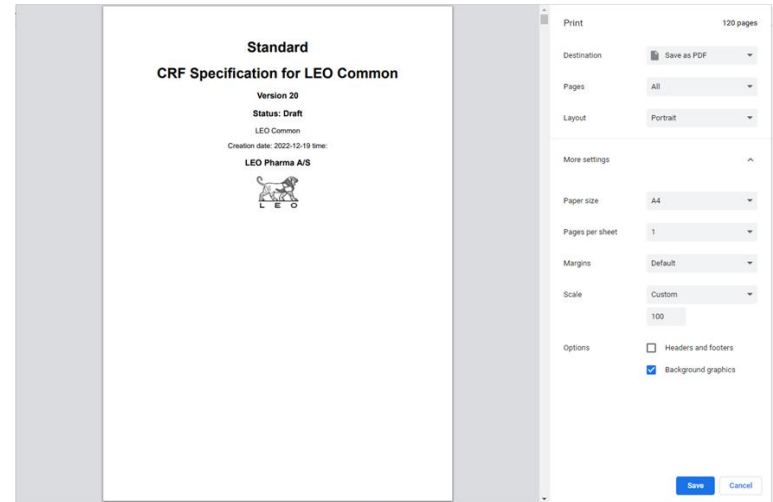
In all browsers, print the HTML renditions as PDF documents to disk as either SDTM annotated CRF specification, define.pdf, acrf.pdf or bcrf.pdf submission documents, etc. Please note:

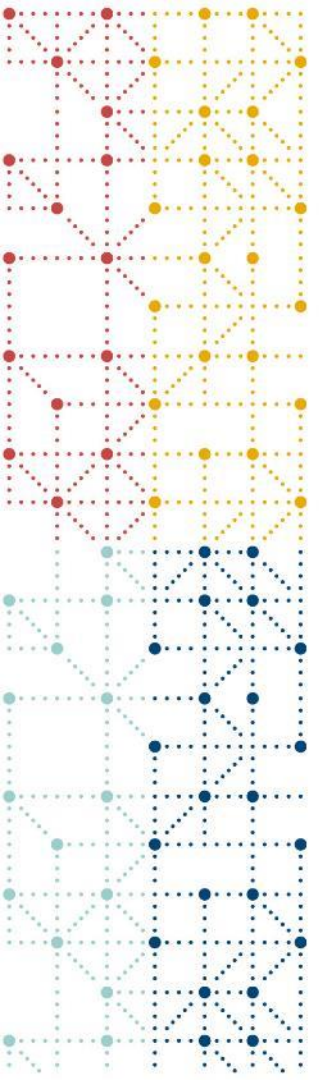
- Headers and footers, portrait versus landscape, and other document properties can be controlled within the printing dialog of your browser.
- Background color(s) requires printing of background graphics to be part of PDF documents.
- The on-screen buttons of the HTML rendition are not included in PDF documents created by printing to a PDF file.
- The TOC/vist matrix will work correctly as navigation links within the PDF documents.
- All SDTM annotations on SDTM annotated CRF documents have link targets available from define-xml, when **Origin** is set to SDTM variable name as Named Destination.

Creating PDF version of ODM-XML

Printing using the browsers standard printing dialog

- Use the engine “Save as PDF”
- Optionally select page subset
- Control headers and footings
- Observe that the CRF is paginated
- Choose Background graphics for the yellow colour for SDTM annotations
- Save as “acrf.pdf” or “bcrf.pdf” when so chosen





Interlinking ODM-XML and Define documents

No changes to define style sheet

Interlinking ODM-XML and Define-XML

ODM-XML is printed as acrf.pdf

- CRF as PDF document is paginated
- Table of contents is live with working links
- All submission variables and SDTM annotations has link targets for define-XML origins
 - Target document is hard coded to “acrf.pdf” residing in the same folder on disk
 - All *DOMAIN.VARIABLE* words have a link target (i.e., DM.BRTHDTC)
 - All words in SDTM annotations have a link target too
- Define-XML origin are defined as “Named Destinations”
 - No need to find/calculate page numbers for references
 - Potentially huge savings in time, cost, effort

Define-XML

Define example showing origins as “Named destinations”, example is DM.BRTHDTC



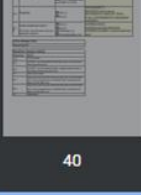
DM (Demographics) - SPECIAL PURPOSE

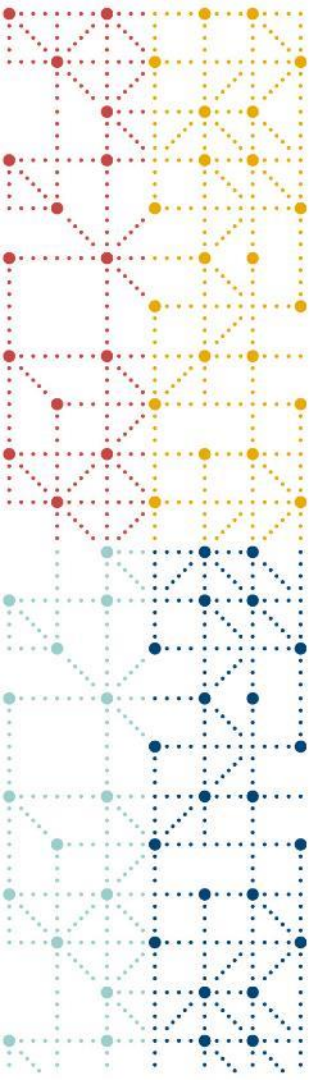
Related Supplemental Qualifiers Dataset: [S4220A](#) (Supplemental Qualifiers DA)

Variable	Label / Description	Type	Role	Length or Display Format	Controlled Term or ISO Format	Origin / Source / Method / Comment
STUDYID	Study Identifier	text	Identifier	200		Protocol
DOMAIN	Domain Abbreviation	text	Identifier		SDTM/Domain Abbreviation [41 Terms]	Assigned
USUBID	Unique Subject Identifier	text	Identifier	200		Derived Concatenation of STUDYID, SUBID, SITEID, separated by underscores when subject naive to submission program. Linked to source
SUBID	Subject Identifier for the Study	text	Topic	200		CRF SDTM annotated CRF (DM.SUBID #)
RFSTDTC	Subject Reference Start Date/Time	datetime	Record Qualifier		ISO 8601	Derived Date/Time of baseline visit
RFENDTC	Subject Reference End Date/Time	datetime	Record Qualifier		ISO 8601	Derived Earliest of non-missing RFXENDTC or RFPENDTC. Linked to source
RFXSTDTC	Date/Time of First Study Treatment	datetime	Record Qualifier		ISO 8601	CRF SDTM annotated CRF (DM.RFXSTDTC #)
RFXENDTC	Date/Time of Last Study Treatment	datetime	Record Qualifier		ISO 8601	CRF SDTM annotated CRF (DM.RFXENDTC #)
RFICDTC	Date/Time of Informed Consent	datetime	Record Qualifier		ISO 8601	CRF SDTM annotated CRF (DM.RFICDTC #)
RFPENDTC	Date/Time of End of Participation	datetime	Record Qualifier		ISO 8601	CRF SDTM annotated CRF (DM.RFPENDTC #)
DTHDTC	Date/Time of Death	datetime	Record Qualifier		ISO 8601	Predecessor: AE.AES1DTC
DTHFL	Subject Death Flag	text	Record Qualifier	1	Yes/No/Reason - "Y" = "Yes" - "N" = "No"	Assigned
SITEID	Study Site Identifier	text	Record Qualifier	200		CRF SDTM annotated CRF (DM.SITEID #)
BRTHDTC	Date/Time of Birth	datetime	Record Qualifier		ISO 8601	CRF SDTM annotated CRF (DM.BRTHDTC #)

Interlinking ODM-XML and Define-XML

acrf.pdf showing link target, example is DM.BRTHDTC

<p>38</p> 		<p>1.1 # Standard Governance Board (SGB) sharepoint site in the folder Date of birth. Note that the list contains information about collection of allowed DOB formats for adults in different countries. In pediatric/adolescent trials and trials in countries not on the list, the trial team must verify the information with NLCRA or trial CRA manager. If Date of birth is transferred from IRT the CRF guidance text should be deleted.</p>	<p>Always collect dates as DD-MMM-YYYY and store dates as ISO8601 in SDTM.</p>	<p><u>DM.BRTHDTC</u></p>	
<p>39</p> 		<p>2.1 Age <(transferred from IRT)> Age only to be collected if full date of birth is not collected. Age on the day informed consent was signed.</p>	<p><input type="text"/> Integer</p>	<p>SUPPDM.QVAL, SUPPDM.QNAM=AGEIC, SUPPDM.QLABEL='Age in years at informed consent'</p>	
<p>40</p> 		<p>2.2 Age unit</p>	<p><input type="radio"/> Year(s) (YEARS)</p>	<p>DM.AGEU</p>	
		<p>3.1 # Sex, determined by the investigator</p>	<p><input type="radio"/> Male (M) <input type="radio"/> Female (F)</p>	<p>DM.SEX</p>	
		<p>3.2 # Ethnicity, self-reported by the subject</p>	<p><input type="radio"/> Hispanic or Latino (HISPANIC OR LATINO) <input type="radio"/> Not Hispanic or Latino (NOT HISPANIC OR LATINO) <input type="radio"/> Not reported (Not</p>	<p>DM.ETHNIC</p>	



Thank You!



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