



Do It Yourself: Case Report Form (CRF) Annotation



Caro Sluijter

Senior Clinical Programmer / PHUSE EU Connect / Belfast

Agenda



- Introduction
- CRF Annotation
 - Annotation V1.0 vs V2.0: Improvements and Points of Attention
 - Linking of Non-Unique CRF Pages
 - Smart CRF Annotation
- CRF Bookmarking
 - Bookmarking V1.0 vs V2.0: Improvements and Points of Attention
 - Smart CRF Bookmarking
- Conclusion



Introduction



Introduction

On 30th of March 2021 the Metadata Submission Guidelines (MSG) team from CDISC updated the MSG V1.0 to V2.0

Clarified some outstanding discussions within our company

At the moment V1.0 and V2.0 are both in use

- V1.0 used to create annotated Case Report Form (aCRF) in older studies
- V2.0 used more often in new studies
- As MSG are guidelines and no rules, not all CRFs are annotated accordingly

How to best annotate a CRF and to raise a few point of attention



CRF Annotation

Annotation V1.0 vs V2.0: Improvements and Points of Attention



Annotation V1.0 vs V2.0: Improvements

We receive aCRFs from our clients:

- CRFs did not look harmonised across clients;
 - Use of different colours for the annotation boxes;
 - Different outlook/style of the content of the boxes.
-
- CRFs looks overcrowded or messy at times

ANNOTATION

ANNOTATION

ANNOTATION



Annotation V1.0 vs V2.0: Improvements

- MSG V1.0: It was generally accepted to use **Red, BOLD, ITALIC** lettering
- MSG V2.0: Now suggested to use Black, Not Bold, Not Italic lettering

DS=Disposition **DSCAT = "PROTOCOL MILESTONE"**
DSTERM/DSDECOD = "INFORMED CONSENT OBTAINED"

INFORMED CONSENT

Informed Consent Date

DM=Demographics **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

Age **AGE** **AGEU** years

Sex ☐ Female ☐ Male **SEX**

DS (Disposition) **DSCAT = PROTOCOL MILESTONE**
DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM (Demographics) **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

Age **AGE** **AGEU** years

Sex ☐ Female ☐ Male **SEX**



Annotation V1.0 vs V2.0: Improvements

- MSG V1.0:
 - Use of quotation marks was accepted
 - Equal sign between domain abbreviation and domain full name
- MSG V2.0:
 - Advised to not use quotation marks
 - Domain full term is now between parentheses

DS=Disposition **DSCAT = "PROTOCOL MILESTONE"**
DSTERM/DSDECOD = "INFORMED CONSENT OBTAINED"

INFORMED CONSENT

Informed Consent Date

DM=Demographics **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

AGE **AGEU**

Age years

Sex ☐ Female ☐ Male **SEX**

DS (Disposition) **DSCAT = PROTOCOL MILESTONE**
DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM (Demographics) **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

AGE **AGEU**

Age years

Sex ☐ Female ☐ Male **SEX**



Annotation V1.0 vs V2.0: Improvements

- MSG V1.0:
 - All box borders were the same
- MSG V2.0:
 - Full border for information 'collected' on the CRF
 - Dashed border for extra information for the reviewer or programmer

DS=Disposition

DSCAT = "PROTOCOL MILESTONE"

DSTERM/DSDECOD = "INFORMED CONSENT OBTAINED"

INFORMED CONSENT

Informed Consent Date

DM=Demographics

DSSTDTC

RFICDTC

DEMOGRAPHICS

Birth Year

BRTHDTC

AGE AGEU

Age years

Sex ☐ Female ☐ Male SEX

DS (Disposition)

DSCAT = PROTOCOL MILESTONE

DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM (Demographics)

DSSTDTC

RFICDTC

DEMOGRAPHICS

Birth Year

BRTHDTC

AGE AGEU

Age years

Sex ☐ Female ☐ Male SEX



Annotation V1.0 vs V2.0: Points of Attention

- Border lines:
- What to do when a value is pre-printed on the CRF?

DS=Disposition **DSCAT = "PROTOCOL MILESTONE"**
DSTERM/DSDECOD = "INFORMED CONSENT OBTAINED"

INFORMED CONSENT

Informed Consent Date

DM=Demographics **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

Age **AGE** **AGEU** years

Sex ☐ Female ☐ Male **SEX**

DS (Disposition) **DSCAT = PROTOCOL MILESTONE**
DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM (Demographics) **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

Age **AGE** **AGEU** years

Sex ☐ Female ☐ Male **SEX**



Annotation V1.0 vs V2.0: Improvements

- MSG V1.0:
 - No guideline for annotation box colours
- MSG V2.0:
 - Recommend to use one of four colours
 - Minimise difficulties for people with colour blindness

DS=Disposition

DSCAT = "PROTOCOL MILESTONE"

DSTERM/DSDECOD = "INFORMED CONSENT OBTAINED"

INFORMED CONSENT

Informed Consent Date

DM=Demographics

DSSTDTC

RFICDTC

DEMOGRAPHICS

Birth Year

BRTHDTC

AGE AGEU

Age years

Sex ☐ Female ☐ Male SEX

DS (Disposition)

DSCAT = PROTOCOL MILESTONE

DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM (Demographics)

DSSTDTC

RFICDTC

DEMOGRAPHICS

Birth Year

BRTHDTC

AGE AGEU

Age years

Sex ☐ Female ☐ Male SEX



Annotation V1.0 vs V2.0: Points of Attention

- Colourblindness
- NOT SUBMITTED

DS=Disposition **DSCAT = PROTOCOL MILESTONE**
DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM=Demographics **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

AGE **AGEU**

Age years

Sex ☐ Female ☐ Male **SEX**

DS (Disposition) **DSCAT = PROTOCOL MILESTONE**
DSTERM / DSDECOD = INFORMED CONSENT OBTAINED

INFORMED CONSENT

Informed Consent Date

DM (Demographics) **DSSTDTC**
RFICDTC

DEMOGRAPHICS

Birth Year **BRTHDTC**

AGE **AGEU**

Age years

Sex ☐ Female ☐ Male **[NOT SUBMITTED]**



CRF Annotation

Linking of Non-Unique CRF Pages



Unique vs Non-Unique CRF pages

MSG V2.0 advises that an aCRF only contains unique CRF pages

- Same data collection points
- Instruction information can differ
- Minor rearrangements of page is allowed

However, in older studies the CRF consists of all forms used per visit (CRF Book)

Advised to only annotate the unique forms and refer when a form is re-used

Question: Are two pages identical when certain information is needed for Visit X, and thus annotated, but not needed for Visit Y and thus not submitted?

Option: Easiest way: Add instructional (dashed border) box on the first CRF page with information on when the information needs to be included in the SDTM



Unique vs Non-Unique CRF pages

Advised to only annotate the unique forms and refer when a form is re-used

Also advised to add a table of content (ToC) for more efficient review process

Question: How do you know the right page to link your non-unique page to?

- Initial Actual PDF page?
- Actual PDF page after ToC is added?

Options:

- Using NamedDestinations? (P21 community does not support this automatically)
- Not using ToC (as not required by FDA)



CRF Annotation

Smart CRF Annotation



Smart CRF Annotation

- Standardisation of the aCRF
 - Library of annotated CRF pages
 - Re-use complete CRF annotation
 - Storing the annotated PDF as XML Forms Data Format (XFDF)
 - XFDF: Stores descriptions of page form elements and their values, such as comments
 - Imported into blank CRF
 - Used for CRF pages in Define-XML

```
<?xml version="1.0" encoding="UTF-8" standalone="no" ?>
<defaultappearance>
  <defaultstyle>
    <font: 'Times New Roman', serif 12.0pt; text-align: left; color: #000000 />
  </defaultstyle>
  </freetext>
  <freetext color="#BFFFFFF" creationdate="D:20181122173818+01'00'" flags="print" date="D:20210624212420+02'00'" name="026c86a8-ab65-45d2-a822-973fca464ab1" page="7" recid="1" />
</contents-richtext>
<body xmlns="http://www.w3.org/1999/xhtml" xmlns:xfa="http://www.xfa.org/schema/xfa-data/1.0/" xfa:APIVersion="Acrobat:10.1.16" xfa:spec="2.0.2" style="font-size: 12pt; font-family: 'Times New Roman'" />
  <p dir="ltr">
    <span style="font-family: 'Times New Roman'" />
    <[NOT SUBMITTED] />
  </p>
</body>
</contents-richtext>
</defaultappearance>
```



Smart CRF Annotation

- Standardisation of the aCRF
 - Library of annotated CRF pages
 - Re-use complete CRF annotation
 - Storing the annotated PDF as XML Forms Data Format (XFDF)
 - XFDF: Stores descriptions of page form elements and their values, such as comments
 - Update Annotations from MSG V1.0 to MSG V2.0 as XFDF also stores
 - Colours
 - Font sizes/types

```
>0 G 0 0 0 rg 0 Tc 0 Tw 100 Tz 0 TL 0 Ts 0 Tr /TimesNewRoman 12 Tf</defaultappearance>
</defaultstyle>
>font: 'Times New Roman', serif 12.0pt; text-align:left; color:#000000 </defaultstyle>
</freetext>
<freetext color="#BFFFFFF" creationdate="D:20181122173818+01'00'" flags="print" date="D:20210624212420+02'00'" name="026c86a8-ab65-45d2-a822-973fca464ab1" page="7" rec
</contents-richtext>
<body xmlns="http://www.w3.org/1999/xhtml" xmlns:xfa="http://www.xfa.org/schema/xfa-data/1.0/" xfa:APIVersion="Acrobat:10.1.16" xfa:spec="2.0.2" style="font-size:12.0
<p dir="ltr"
<span style="font-family:'Times New Roman'"
>[NOT SUBMITTED]</span>
</p>
</body>
</contents-richtext>
</defaultappearance>
```



CRF Bookmarking

Annotation V1.0 vs V2.0: Improvements and Points of Attention



Bookmarking V1.0 vs V2.0: Improvements

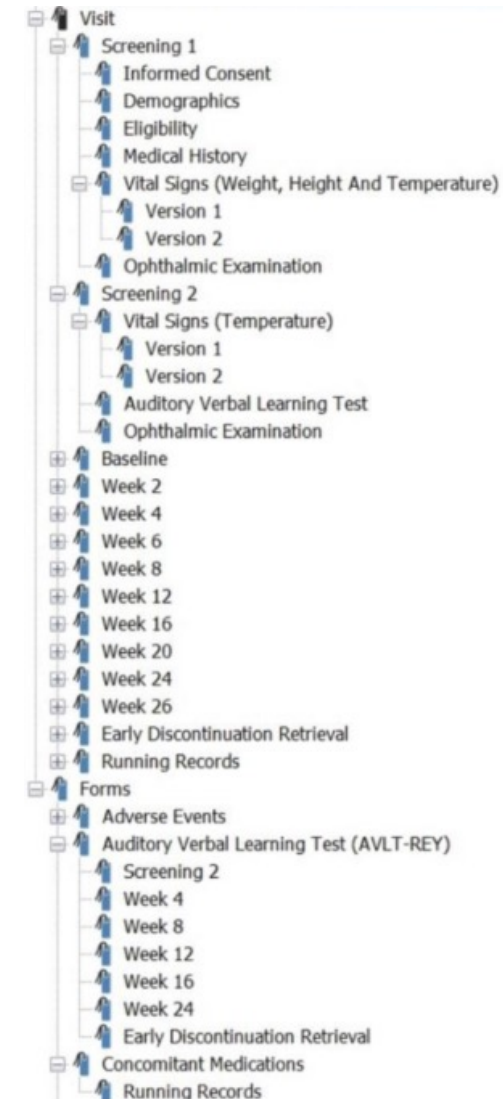
- Dual Bookmarking
 - V1.0: By Chronology and By Domain
 - V2.0: By Chronology and By CRF Topic/Form
- CRF form will be bookmarked as many times as it is used during a study (for each visit).





Bookmarking V1.0 vs V2.0: Points of Attention

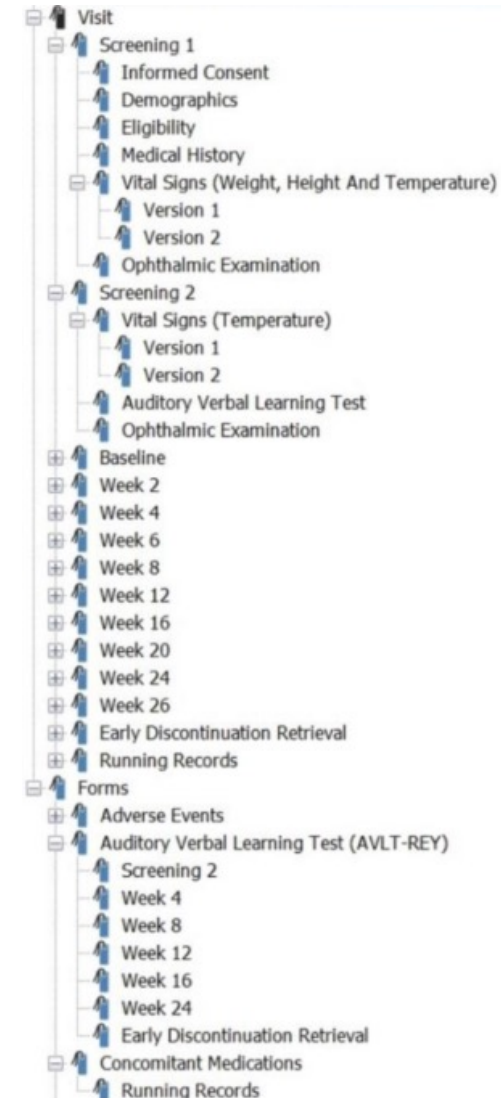
- Using the CRF Topic/Form name as bookmark description
 - Long
 - Not Informative
- Recommendation
 - Keeping form names in mind during CRF design
 - Use descriptive CRF form names





Bookmarking V1.0 vs V2.0: Points of Attention

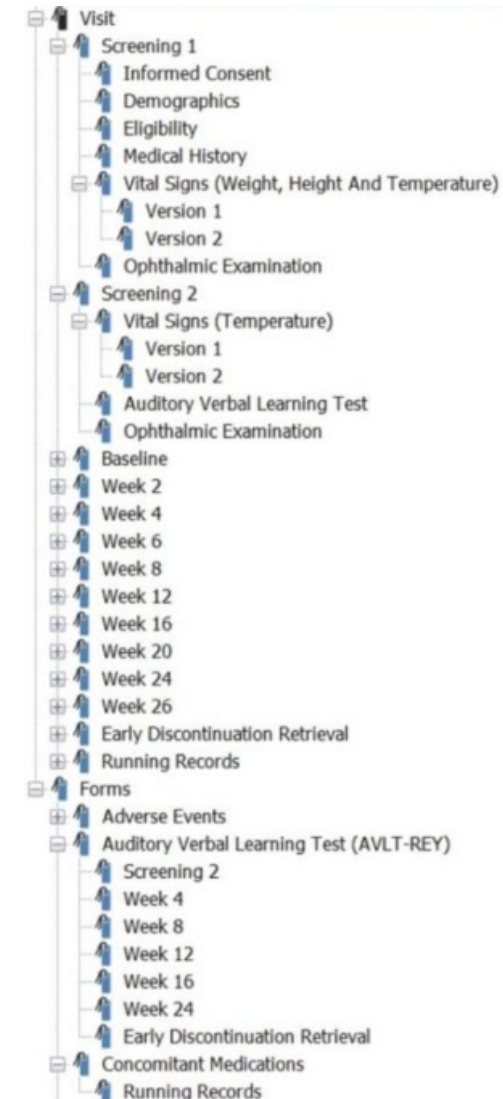
- Unique CRF page is bookmarked for every visit it is used in
 - Labor-intensive
 - Feels redundant
- Option?
 - Way to create 1 bookmark for all visits that refer to the same page?
 - Bookmarking tool





Bookmarking V1.0 vs V2.0: Points of Attention

- How to bookmark first bookmarks in hierarchy?
 - “Visits” / “Forms”
- Recommendation
 - Kept empty
 - Bookmark to the first CRF page that is used in the hierarchy
 - Bookmark to first page of CRF
- All are valid options, would like one option for harmonisation of CRF bookmarks across aCRFs and Sponsors





CRF Bookmarking

Smart CRF Bookmarking



Smart CRF Bookmarking

- Bookmarking
 - Simple task but repetitive with a lot of pointing and clicking → Time-consuming
 - Use XML export functionality
 - Information on
 - CRF page of bookmark
 - Fitetype (Zoom level)
 - Zoom
 - Color and Style

```
<?xml version="1.0" encoding="UTF-8" ?>
- <BOOKMARKS>
- <ITEM NAME="Visit" PAGE="70" FITETYPE="XYZ" ZOOM="0.000000" VIEWRECT="Left=-0.000008;Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="0">
- <ITEM NAME="Screening" PAGE="70" FITETYPE="XYZ" ZOOM="0.000000" VIEWRECT="Left=-0.000008;Top=841.979980" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="1">
  <ITEM NAME="SignContract registration form" PAGE="70" FITETYPE="FitH" ZOOM="0" VIEWRECT="Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="2" />
  <ITEM NAME="Demographic registration form" PAGE="28" FITETYPE="XYZ" ZOOM="0.000000" VIEWRECT="Left=0.000000;Top=841.980103" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION=""
    Open="true" INDENT="2" />
</ITEM>
- <ITEM NAME="Visit 1" PAGE="8" FITETYPE="FitH" ZOOM="0" VIEWRECT="Top=841.799988" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="1">
  <ITEM NAME="BP_HR_sup registration form" PAGE="8" FITETYPE="FitH" ZOOM="0" VIEWRECT="Top=841.799988" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="2" />
</ITEM>
- <ITEM NAME="Running Records" PAGE="2" FITETYPE="XYZ" ZOOM="1.178610" VIEWRECT="Left=0.000000;Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true"
  INDENT="1">
  <ITEM NAME="AE registration form" PAGE="2" FITETYPE="XYZ" ZOOM="1.178610" VIEWRECT="Left=0.000000;Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true"
    INDENT="2" />
</ITEM>
</ITEM>
```



Smart CRF Bookmarking

- XML Bookmarking as a tool
 - FDA requires the bookmarks to have zoomlevel “Inherit Zoom”
 - Need to be updated per bookmark
- Or
 - Update the FITETYPE to be equal to “XYZ” in the XML file and import that XML file in CRF

```
<?xml version="1.0" encoding="UTF-8" ?>
- <BOOKMARKS>
- <ITEM NAME="Visit" PAGE="70" FITETYPE="XYZ" ZOOM="0.000000" VIEWRECT="Left=-0.000008;Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="0">
- <ITEM NAME="Screening" PAGE="70" FITETYPE="XYZ" ZOOM="0.000000" VIEWRECT="Left=-0.000008;Top=841.979980" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="1">
  <ITEM NAME="SignContract registration form" PAGE="70" FITETYPE="FitH" ZOOM="0" VIEWRECT="Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="2" />
  <ITEM NAME="Demographic registration form" PAGE="28" FITETYPE="XYZ" ZOOM="0.000000" VIEWRECT="Left=0.000000;Top=841.980103" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION=""
    Open="true" INDENT="2" />
</ITEM>
- <ITEM NAME="Visit 1" PAGE="8" FITETYPE="FitH" ZOOM="0" VIEWRECT="Top=841.799988" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="1">
  <ITEM NAME="BP_HR_sup registration form" PAGE="8" FITETYPE="FitH" ZOOM="0" VIEWRECT="Top=841.799988" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true" INDENT="2" />
</ITEM>
- <ITEM NAME="Running Records" PAGE="2" FITETYPE="XYZ" ZOOM="1.178610" VIEWRECT="Left=0.000000;Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true"
  INDENT="1">
  <ITEM NAME="AE registration form" PAGE="2" FITETYPE="XYZ" ZOOM="1.178610" VIEWRECT="Left=0.000000;Top=841.980042" COLOR="0,0,0" STYLE="notbold,notitalic" ACTION="" Open="true"
    INDENT="2" />
</ITEM>
</ITEM>
```



Smart CRF Bookmarking

- XML Bookmarking as a tool
 - Take this further
 - Creation of bookmark XML FILE from scratch
 - Custom made spreadsheet to enter the bookmarks
 - Using SAS to create the XML code that we can save as an XML file
 - More convenient and less manual labor

Nr	Forms	Page	Not Submitted	Screening	Visit 1	Visit 2	Follow-up	Running Records
1	Adm_IV registration form				x			
2	AE registration form							x
3	Appoint registration form			x		x		
4	Arrival registration form			x	x		x	
5	BegUrCol registration form				x			
6	Bladder registration form				x			
7	BP_HR_sup registration form			x	x	x	x	

```
INDENT = 2 />  
</ITEM>  
</ITEM>
```



Conclusion

Conclusion



- Very happy with the updated MSG V2.0
- Clarity for annotation and bookmarking
- Still need to take into account the preferences of the sponsors and CRO's
- Good to have guidelines and not strict rules

Thank You!



- For more information about CRF annotation, CRF bookmarking or the CRF tool:
 - Please feel free to contact info.nl@ocs-consulting.com
 - Visit our OCS Life Science booth after the session

- OCS Life Science @ PHUSE:
 - CT05 – CALL EXECUTE will figure it out: Data-driven Figure Programming
 - PP23 – SanityCheckR: Data Quality Control with R Shiny
 - SI05 – Maturing Standardisation: The Switch from Spreadsheet-Based Standards to an MDR
 - TT14 – The Impact of Migrating to SAS Viya 202X (aka SAS Viya 4)

Caro Sluijter, Senior Clinical Programmer
OCS Life Sciences
Caro.Sluijter@ocs-consulting.com