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Integrated Process of aCRF with Dual Bookmarking and TOC for SDTM-MSG-V2.0

Presented by:
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EVEREST
CLINICAL RESEARCH

Meet the Speakers

Xinran Luo

Title: Statistical Programmer II

Organization: Everest Clinical Research Co.

Xinran Luo is a statistical programmer at Everest Clinical Research with 3 years of experience. She graduated from Columbia University with a Master of Public Health degree and Applied Biostatistics certificate. In addition to the daily programing tasks, she supports the development and testing of CDISC standardization tool within the organization.

Shuang Qiu

Title: Statistical Programmer II

Organization: Everest Clinical Research Co.

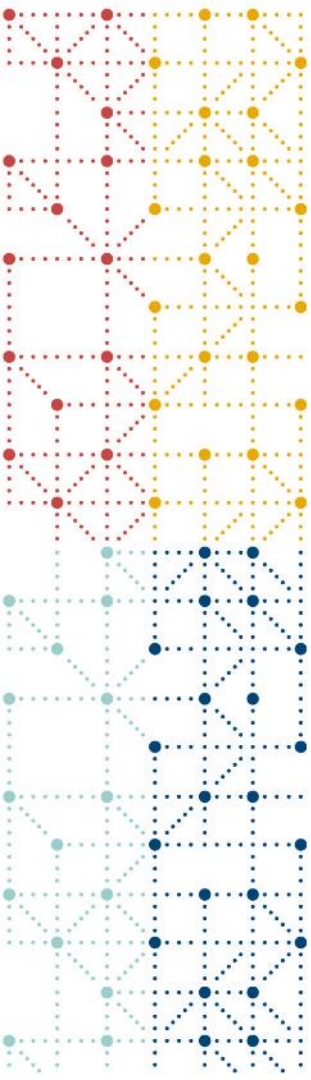
Shuang has received her M.S. degree in biostatistics from University of Toronto. She is working as a statistical programmer at Everest Clinical Research with 4 years of industry experience. Her focus is providing outstanding quality, on-time delivery, and exceptional customer service to clinical research partners.

Disclaimer and Disclosures

- *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.*

Agenda

1. Introduction of aCRF
2. Basic Principles for Annotation
3. The Changes in SDTM-MSG V2.0
4. Integrated process of generating an annotated CRF with dual bookmarking and TOC that meets the SDTM-MSG-V2.0 standard
5. Q & A



Introduction of aCRF

aCRF (Annotated CRF) Introduction

- **Definition**:
- The annotated
  clinical data c
  the correspon
  Datasets”

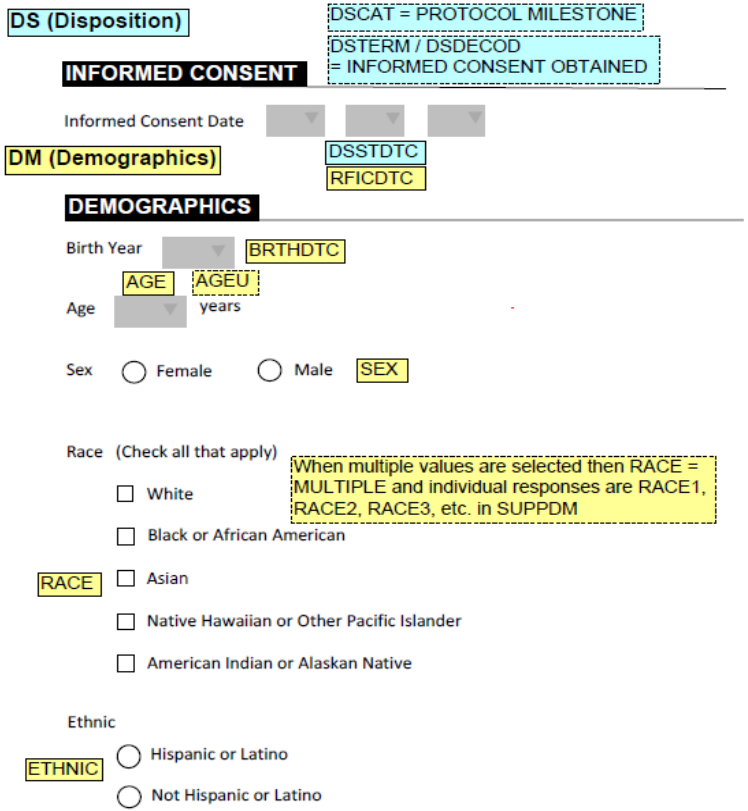
- **Contents**:
- It describes th
  dataset, varial
  recommended
  and table of c
  data collectior

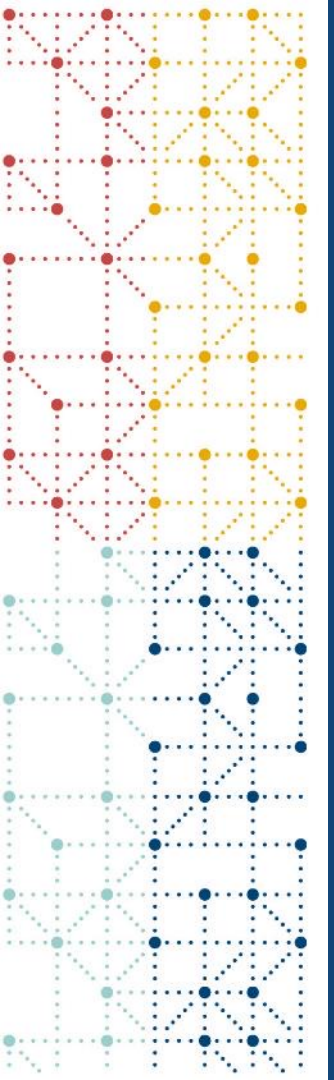
- **Purpose:**
- It helps suppc
  the SDTM dat

nt that maps the
electronic or paper) to
within the SDTM

corresponding SDTM
the CRF. It is
d. Dual bookmarking
with an overview of the

cies; It helps prepare





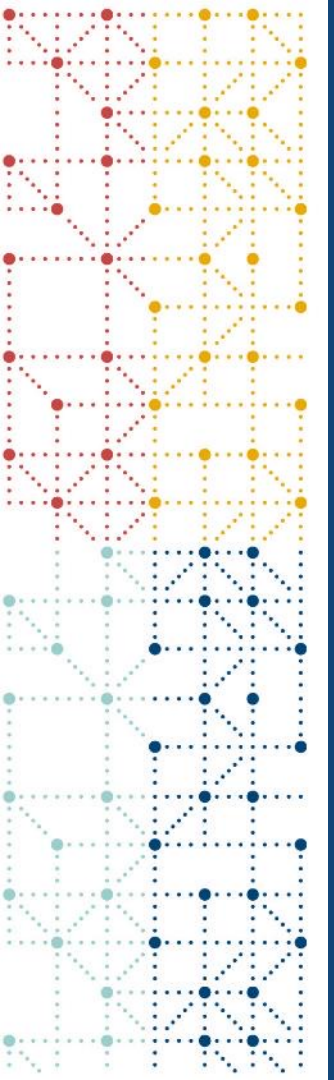
Basic Principles for Annotations

Basic Principles for Annotations

- The annotations should be **searchable**
- The annotations should reflect the data that are expected to be submitted within the SDTM. In the event that data were intended to be collected for a variable, but none actually was, the annotated CRF will represent the data that would have been submitted.
- If the data are recorded on the CRF but are not submitted in SDTM, the CRF be annotated with the text “NOT SUBMITTED”.
- All text in the annotations that represent variable and domain names should be capitalized.
- The Annotations should not obstruct any text on the CRF page.

Basic Principles for Annotations

- Each domain that is represented on a CRF page should have its own annotation on the left side of the CRF page with the 2-letter domain code and domain name. Note that domain names rather than dataset names are annotated, e.g., SUPPQUAL, Split Domains.
- If more than one domain exists on a page as each domain annotation, and all its variables, should be color-coded.
- Relationship data collected on CRF pages and documented in RELREC should be annotated.
- Partial CRF page annotations should be avoided.
- Quotation mark is not recommended to use (e.g., expressed as DSCAT = PROTOCOL MILESTONE instead of DSCAT = "PROTOCOL MILESTONE").



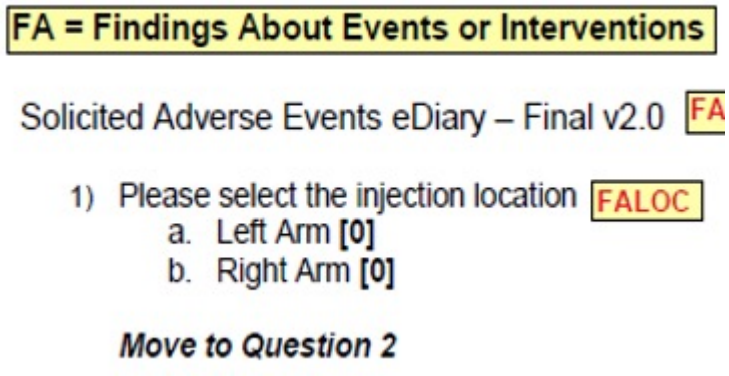
The Changes in SDTM-MSG V2.0

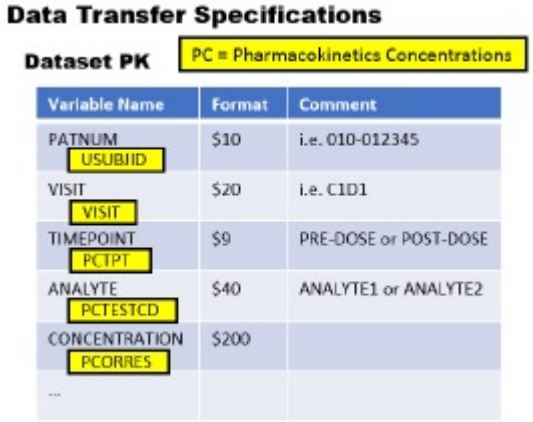
The Changes in SDTM-MSG V2.0

SDTM-MSG V2.0 was Released on Mar 30, 2021

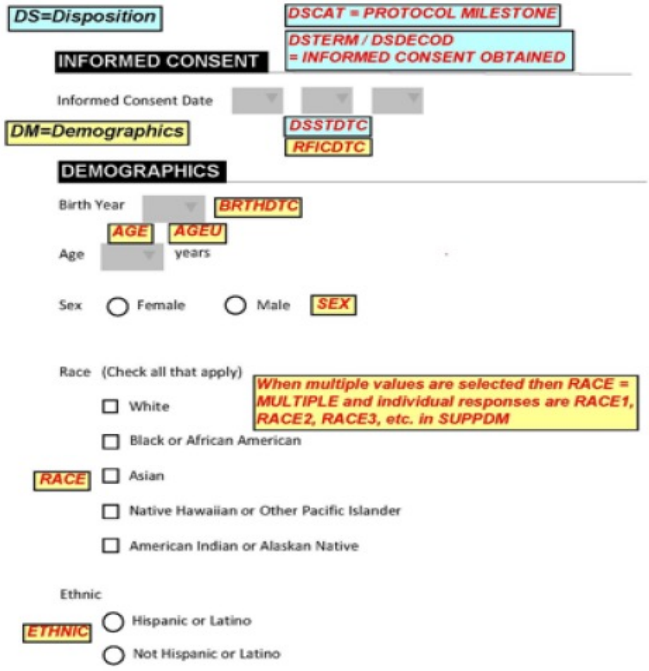
Contents Update:

- Annotating CRF pages is not limited to traditional paper and eCRFs. The nontraditional digital devices (e.g. ePROs, eDiary), the corresponding collection screens should be appended to the end of the traditional eCRF.
- The annotations of external data transfer specification (e.g. laboratory or ECG) is also recommended to append to the end of the aCRF.

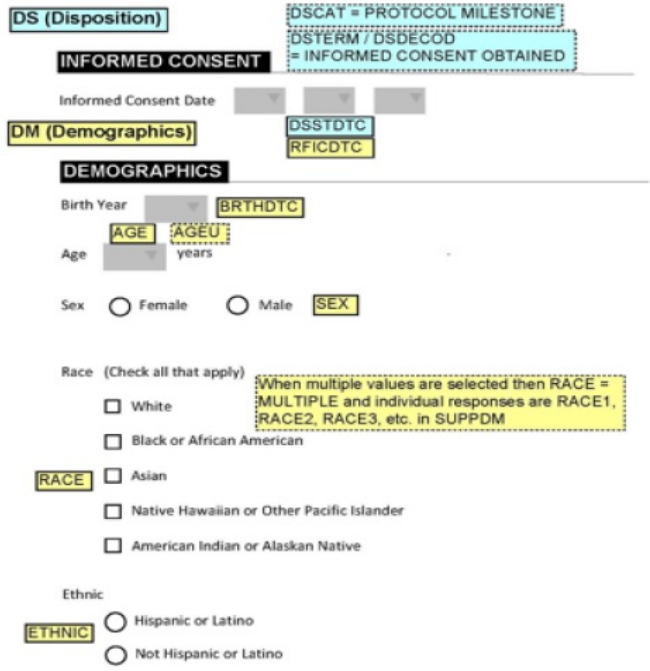




SDTM-MSG v1.0 Annotation Style



SDTM-MSG v2.0 Annotation Style



The Changes in SDTM-MSG V2.0

Example 1: Domain and Variables Appearance

SDTM-MSG V1.0

DM = Demographics

D7220C00001_Version_2.0_20JUL2021: Unique Forms

Project Name: D7220C00001

Form: Subject Identification

Generated On: 20 Jul 2021 11:01:02

Site ID *(integrated, no entry required)*	SITEID
Subject Number *(derived, no entry required)*	SUBJNUM in SUPPDM
Subject ID *(integrated, no entry required)*	SUBJID

SDTM-MSG V2.0

DM (Demographics)

DEV_EVERESTSTANDARDSTUDY_Draft 1.0_28APR2023: All CRFs

Project Name: EVEREST STANDARD STUDY

Form: Subject Identification

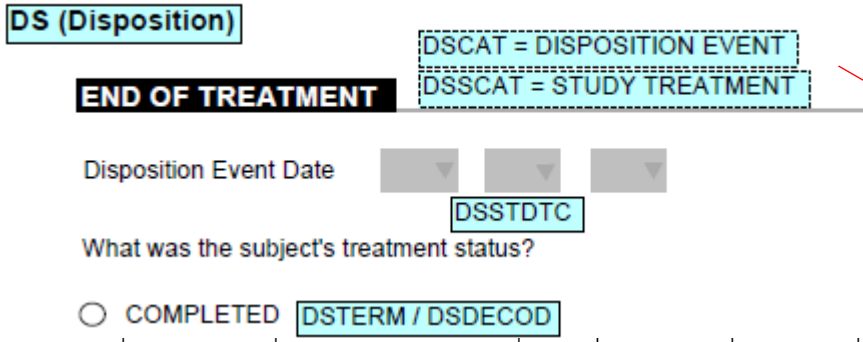
Generated On: 03 May 2023 21:17:07

Site ID	SITEID
Subject No.	[NOT SUBMITTED]
Subject ID	SUBJID

The Changes in SDTM-MSG V2.0

Example 2: Not Direct Variables - Assigned Variables Annotation

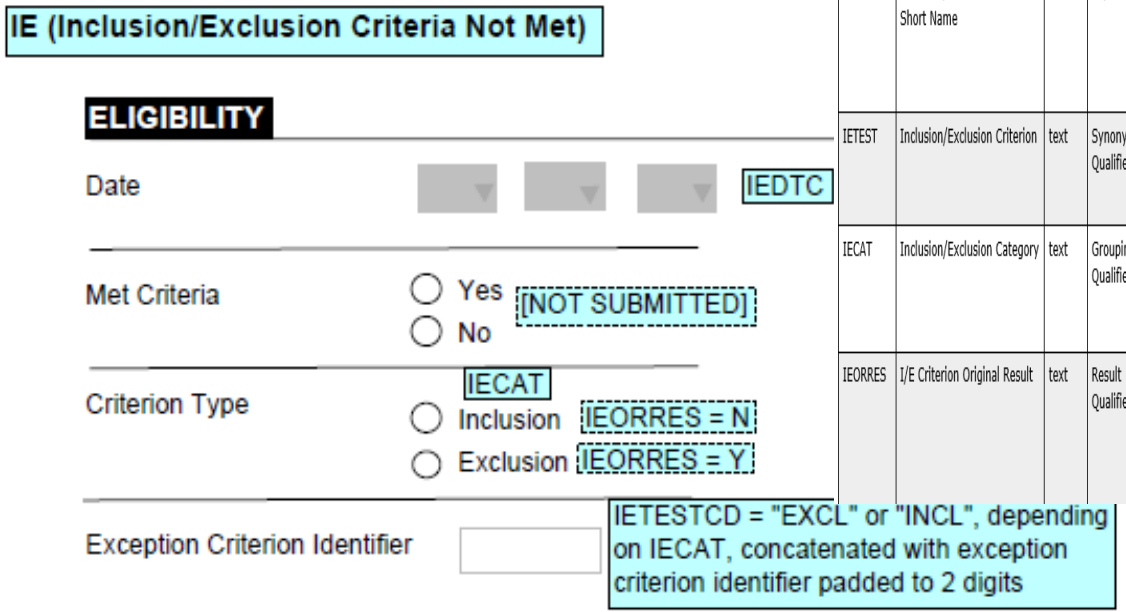
- -CAT and –SCAT , meaningful annotations are required for a single domain on a CRF module
- –CAT and –SCAT annotation are put on top to the form



DSCAT		Category for Disposition Event	text	Grouping Qualifier	18	Category for Disposition Event • "DISPOSITION EVENT" = "Disposition Event" • "PROTOCOL MILESTONE" = "Protocol Milestone"	Assigned (Source: Sponsor) Annotated CRF [5 27 28] Variable is Assigned but there are annotations to help understand the data and so references to the proper pages are included

The Changes in SDTM-MSG V2.0

Example 3: Not Direct Variables – Derived Variables Annotation

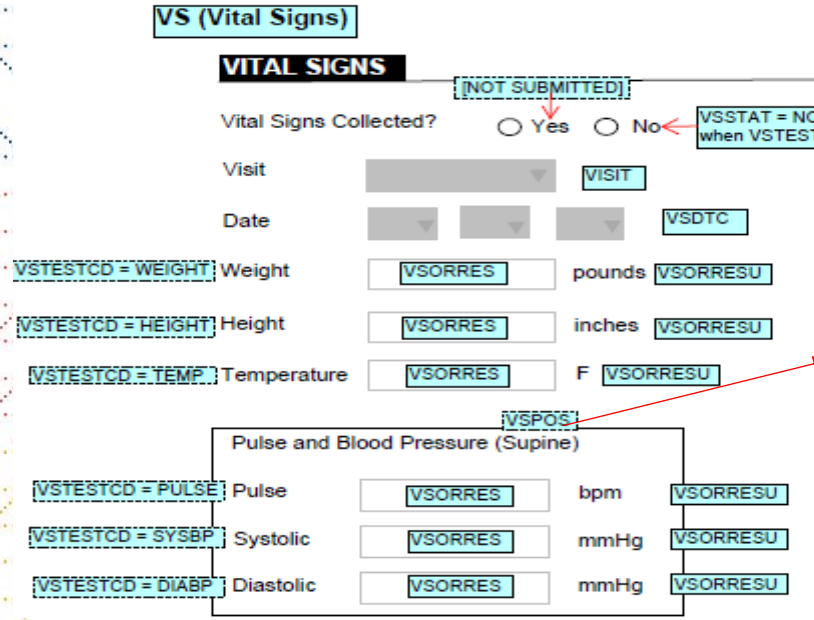


IETESTCD	Inclusion/Exclusion Criterion Short Name	text	Topic	7	Incl/Excl Criterion Short Name [33 Terms]	Collected (Source: Investigator) Annotated CRF [6] Please see Appendix 1 of the cSDRG for complete versions of IETESTCD and IETEST.
IETEST	Inclusion/Exclusion Criterion	text	Synonym Qualifier	196	Inclusion/Exclusion Criterion [33 Terms]	Assigned (Source: Sponsor) Please see Appendix 1 of the cSDRG for complete versions of IETESTCD and IETEST.
IECAT	Inclusion/Exclusion Category	text	Grouping Qualifier	9	Category for Inclusion/Exclusion • "EXCLUSION" = "Exclusion" • "INCLUSION" = "Inclusion"	Collected (Source: Investigator) Annotated CRF [6]
IEORRES	I/E Criterion Original Result	text	Result Qualifier	1	No Yes Response, subset for variables with only "Y" or "N" val • "N" = "No" • "Y" = "Yes"	Derived (Source: Sponsor) Annotated CRF [6] If IECAT=INCLUSION then IEORRES=N, else if IECAT=EXCLUSION then IEORRES=Y

- Dashed box is used for [NOT SUBMITTED]
- Derived variable IEORRES with condition use dashed box

The Changes in SDTM-MSG V2.0

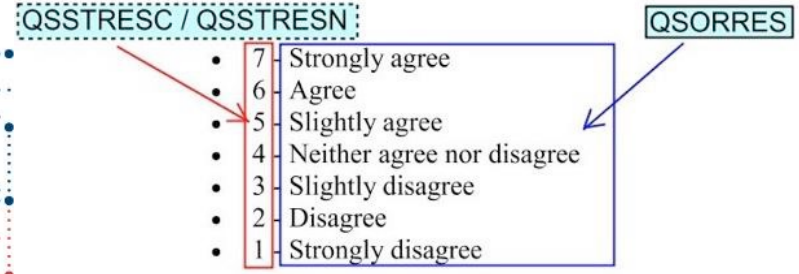
Example 4: Not Direct Variables – Assigned Variables Annotation



VSTEST		Vital Signs Test Name	text	Synonym Qualifier	24	Vital Signs Test Name [6 Terms]	Assigned (Source: Sponsor)
VSPOS		Vital Signs Position of Subject	text	Record Qualifier	8	Position, subset to be used for VSPOS • "STANDING" = "Standing" • "SUPINE" = "Supine"	Assigned (Source: Sponsor) Annotated CRF [8 9 10 11 12 13]

- Variables are assigned if explicitly defined in CRF, annotation is needed
- Arrows, lines, boxes- can be used to further clarify
- NOT DONE is prespecified on the CRF and to be annotated to –STAT with the specified --TESTCD

The Changes in SDTM-MSG V2.0
Example 5: Annotation QS (Questionnaires)

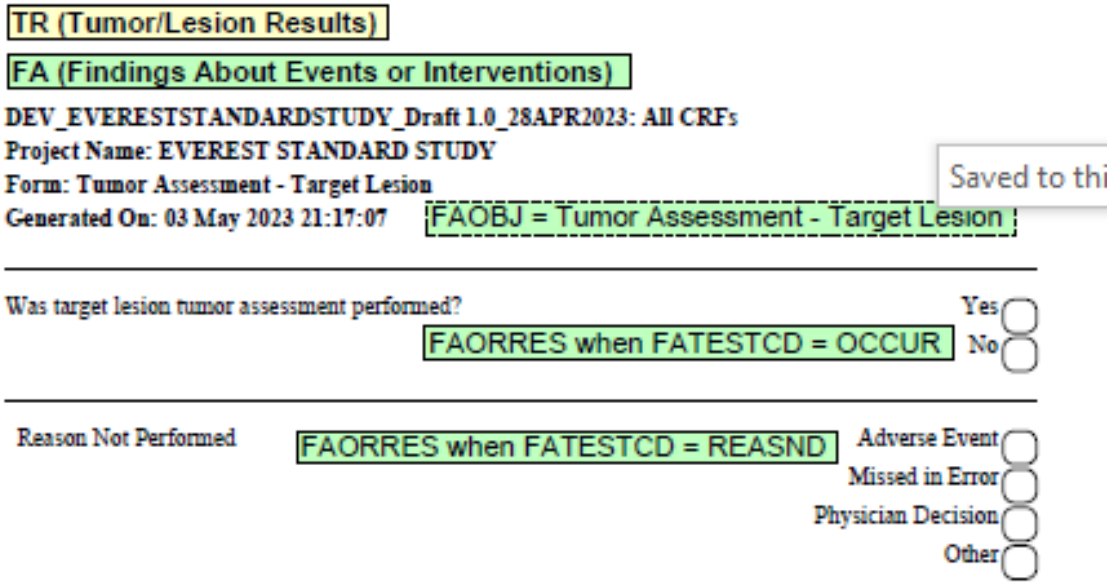


QSORRES	Finding in Original Units	text	Result Qualifier	26	SWLS-Responses [7 Terms]	Collected (Source: Investigator) Annotated CRF [16]
QSSTRESC	Character Result/Finding in Std Format	text	Result Qualifier	1	SWLS-Responses Standardized [7 Terms]	Derived (Source: Sponsor) Annotated CRF [16] If QSORRES="Strongly disagree" then 1 If QSORRES="Disagree" then 2 If QSORRES="Slightly disagree" then 3 If QSORRES="Neither agree nor disagree" then 4 If QSORRES="Slightly agree" then 5 If QSORRES="Agree" then 6 If QSORRES="Strongly agree" then 7
QSSTRESN	Numeric Finding in Standard Units	integer	Result Qualifier	8		Derived (Source: Sponsor) Annotated CRF [16] If QSSTRESC is numeric then QSSTRESN=QSSTRESC in numeric format, else null.

- **When multiple variables are annotated within the same annotation, “ / “ is used to separate the variables**

The Changes in SDTM-MSG V2.0

Example 7: Findings About



- For any CRF data mapped to FA, the annotation of FAORRES should also indicate the corresponding FATESTCD and FAOBJ

The Changes in SDTM-MSG V2.0

Example 8: Conditional Variable

Ongoing	AEENRTPT = ONGOING when Yes is selected where AEENTPT = END OF STUDY	Yes ☐ No ☐

- If “Ongoing” at a study defined reference period can be ticked on the CRF, this information should be stored in the variables --ENTPT and --ENRTPT. The “Ongoing” is annotated to --ENRTPT, while --ENTPT specifies the corresponding reference period

Reprogram ☐

Other Action Taken	AEACNOTH, concatenate when multiple selected
None	AEACNOTH = NONE if selected
Surgery	AEACNOTH = SURGERY if selected
Other	AEACNOTH = OTHER if selected
Other Specify	ACNOTHSP in SUPPAE

- The variable is in conjunction with the condition should be annotated

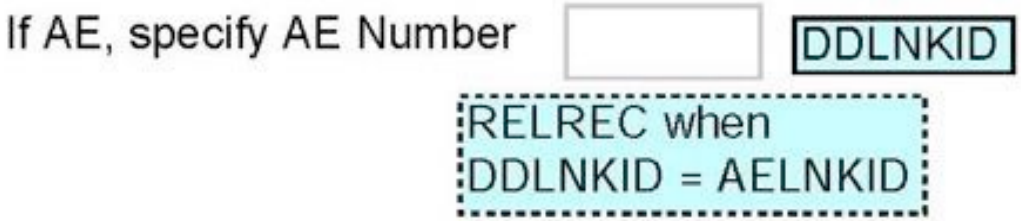
The Changes in SDTM-MSG V2.0

Example 9: Supplemental Qualifiers

- When annotating supplemental qualifier variables, annotate the QNAM value and the supplemental qualifier domain (e.g., "RACEOTH in SUPPDM")

The Changes in SDTM-MSG V2.0

Example 10: RELREC



- When a form indicates a relationship between collected data, the annotations should indicate the collection as well as the RELREC relationship.
- The example shows the death details page where the AE ID number is collected as DDLNKID, which is related to an AE.

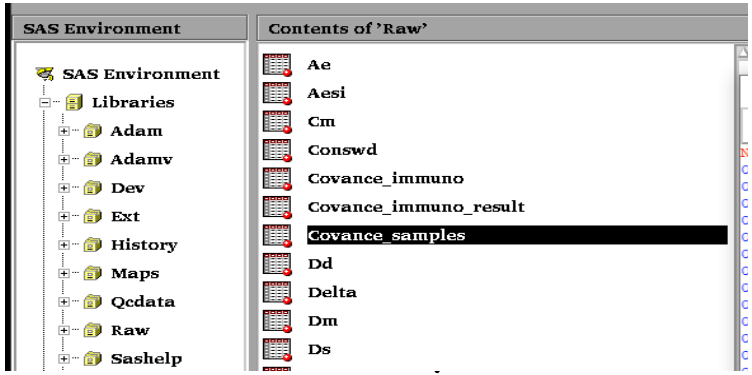
Integrated process of generating an annotated CRF with dual bookmarking and TOC that meets the SDTM-MSG-V2.0 standard

Preparing SDTM CRF Mapping

- Download SDTM specification template
- Follow SDTM IG to determine the correct mapping of CRF fields to SDTM domains, variables, and discrete variable values (e.g. –ORRES in finding domains or –QVAL in supplemental qualifier domains)
- Tips of checking datasets with the mapping forms:
  - ✓ Run proc contents on all raw datasets
  - ✓ Run pdftotext -raw -layout acrf.pdf acrf_to_text.csv
  - ✓ Load acrf_to_text.csv, extract form and page
  - ✓ Merge datapagename from the datasets with the form extracted from blank CRF (or acrf.pdf)
  - ✓ Create final output with Raw dataset, CRF form name, Page number

Preparing SDTM CRF Mapping

Step 1: Run proc contents to retrieve raw dataset contents




```
proc contents data=raw._all_ out=rawdata noprint;
run;

proc sort data=rawdata
          (keep=memname name label type format
                informat length nobs varnum);
  by memname varnum;
run;
```

From RAVE database, DATAPAGENAME contains eCRF page name which should match CRF form name printed on PDF

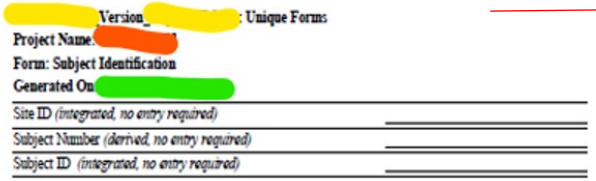
SAS:

File Edit View Tools Data Solutions Help

	MEMNAME	NAME	TYPE	LENGTH	VARNUM	LABEL	FORMAT	INFORMAT	NOBS
10	AE	SITENUMBER	2	50	10	SiteNumber	$	$	542
11	AE	SITEGROUP	2	40	11	SiteGroup	$	$	542
12	AE	INSTANCEID	1	8	12	Internal id for the instance			542
13	AE	INSTANCENAME	2	255	13	Folder instance name	$	$	542
14	AE	INSTANCEREPEATNUMBER	1	8	14	InstanceRepeatNumber			542
15	AE	FOLDERID	1	8	15	Internal id for the folder			542
16	AE	FOLDER	2	50	16	Folder OID	$	$	542
17	AE	FOLDERNAME	2	255	17	Folder name	$	$	542
18	AE	FOLDERSEQ	1	8	18	Folder sequence number			542
19	AE	TARGETDAYS	1	8	19	Target days from study start			542
20	AE	DATAPAGEID	1	8	20	Internal id for data page			542
21	AE	DATAPAGENAME	2	255	21	eCRF page name	$	$	542
22	AE	PAGEREPEATNUMBER	1	8	22	Sequence number of eCRF page in folder			542
23	AE	RECORDDATE	1	8	23	Clinical date of record (ex: visit date)	DATETIME	DATETIME	542

Preparing SDTM CRF Mapping

Step 2: Extract CRF form and page number from PDF



Unix command: pdftotext -raw -layout acrf.pdf acrf_to_text.csv


```
-rw-rw----   1 wyang    studies    60009 Feb 22 14:44 Variables.csv
35 /export/home/wyang/acrf(ferrari)% pdftotext -raw -layout acrf.pdf acrf_to_text.csv
36 /export/home/wyang/acrf(ferrari)% ls -al
total 16002
```

```
** load
acrf_to_text.csv;
proc import out= acrf
   datafile =
"&indir./&infile"
   dbms = csv
   replace;
      getnames=no;
      guessingrows =
1000;
run;
```

	form	page
1	Subject Identification	1
2	Date of Visit	2
3	Screening Date of Visit	3
4	Unscheduled Visit	4
5	Demography	5

```
** identify form with the page number;
** this is RAVE form design pattern;
data forms(keep=form page);
  set acrf;
  length form $200 ;
  retain form;
  if upcase(scan(var1, 1, ':')) ='FORM'
then do;
    form  = strip(substr(var1, 6));
  end;
  if prxmatch("/\d+ of \d+/", var1) then
do;
    page = input(scan(var1, 1), best.);
    output;
  end;
  label form = 'Form'
        page = 'Page';
run;
```

Preparing SDTM CRF Mapping

Step 3: Retrieve form name from each raw dataset

```
** identify dataset from CRF form;
** RAVE study has variable DataPageName;
proc freq data=rawdata noprint;
   tables memname/out=form(drop=percent
                                    count);
    where name eq "DataPageName" and
nobs>0;
run;

** Count number of rawdata from CRF form;
proc sql noprint;
  select count(distinct memname) into :n
    from form
quit;
%let ns = %eval(&n);
proc sql noprint;
  select distinct memname into :set1 - :set&ns
    from  form;
quit;
```

```
**Retrieve form name from each raw dataset;
%macro get_form(din=);
 %do i=1 %to &ns;
   proc sql noprint;
     select datapagename into :form&i
       from raw.&&set&i;
   quit;
 %end;

 data allforms;
  length dset form $100;
   %do i=1 %to &ns;
      dset = "&&set&i";
      form = "&&form&i";
      output;
   %end;
  run;
%mend get_form;
%get_form;
```

dset	form
AE	Adverse Events
AESI	AESI 1 ALTERED SENSATION BOTH HA 16Sep2021
CM	Concomitant Medications
CONSWD	Withdrawal of Informed Consent
DD	Death Details
DM	Demography

Preparing SDTM CRF Mapping

Step 4: Merge datasets between rawdata and CRF extraction

```
proc sort data=rawdata out=all(keep=memname)
nodupkey;
  by memname;
run;

data all;
  merge all(rename=(memname=dset))
        allforms;
  by dset;
run;

proc sql noprint;
 create table final as
  select a.dset label ='Raw Data',
         coalesce(a.form, b.form) as form label = 'CRF Form',
          b.page label = 'Page Number'
    from all as a full join forms as b
     on a.form=b.form
      order by a.dset, form;
quit;
```

```
proc export data = final
        outfile = "rawinfo.xlsx"
        dbms = xlsx
        label
        replace
        ;
run;
quit;
```

Preparing SDTM CRF Mapping

Step 5: Create final form dataset with raw dataset, CRF form name and page number

	A	B	C	D
1	Raw Data	CRF Form	Page Number	SDTM Domain
2		Overdose Report	35	
3		Serious Adverse Events	21	
4		Serious Adverse Events	20	
5	AE	Adverse Events	18	
6	AE	Adverse Events	19	
7	AESI	Adverse Event of Special Interest	22	
8	CM	Concomitant Medications	25	
9	CM	Concomitant Medications	27	
10	CM	Concomitant Medications	26	
11	CM	Concomitant Medications	24	
12	CM	Concomitant Medications	28	
13	CONSWD	Withdrawal of Informed Consent	45	
14	CONSWD	Withdrawal of Informed Consent	46	
15	COVANCE_IMMUNO			
16	COVANCE_SAMPLES			
17	DD	Death Details	23	

A

B

After complete SDTM mapping, all metadata information should be displayed in this index file. Now you can create another column as "SDTM Domain", the advantages are

- **Include all raw datasets**
- **Include all CRF form**
- **Some raw datasets can be from external data without CRF form, see case B**
- **Some CRF form may be missing corresponding raw dataset, see case A – need to confirm with DM**

Semi-automated Annotation

- A semi-automated annotation process can standardize the CRF generation procedure across different studies, eliminate manual issues and provide high efficiency
- Populate the CRF Page where each corresponding mapped SDTM field is collected in the Origin field of the study SDTM specifications
- Export the SDTM specifications to three CSV files.
- Import the SDTM metadata CSV files into SAS
- Import the XFDF file into the CRF PDF file in Adobe Acrobat

Semi-automated Annotation

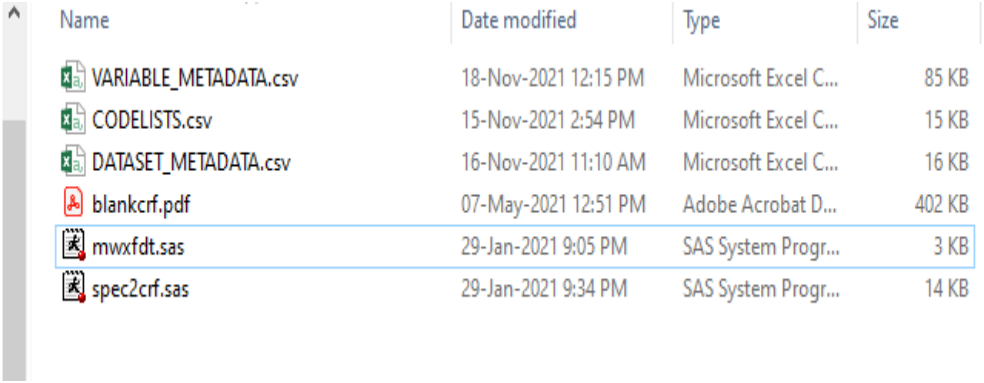
Step 1: Populate the CRF page where each corresponding mapped SDTM field is collected in the Origin field of the study SDTM specifications

- Prior to the import, we need to complete the Origin page field in the SDTM specifications.
- CRF fields that have a 1:1 mapping to an SDTM variable should have the CRF page listed in the Origin field of the corresponding SDTM Domain (e.g., the “AE” sheet of the SDTM specifications).

Semi-automated Annotation

Step 2: Export the SDTM specifications to three CSV files

Create three CSV files named "DATASET_METADATA.csv", "VARIABLE_METADATA.csv", and "VALUE_METADATA.csv". These files are similar to the structure of define.xml data specification, "Datasets", "Variables" and "ValueLevel" tab.



Name	Date modified	Type	Size
VARIABLE_METADATA.csv	18-Nov-2021 12:15 PM	Microsoft Excel C...	85 KB
CODELISTS.csv	15-Nov-2021 2:54 PM	Microsoft Excel C...	15 KB
DATASET_METADATA.csv	16-Nov-2021 11:10 AM	Microsoft Excel C...	16 KB
blankcrf.pdf	07-May-2021 12:51 PM	Adobe Acrobat D...	402 KB
mwxfdt.sas	29-Jan-2021 9:05 PM	SAS System Progr...	3 KB
spec2crf.sas	29-Jan-2021 9:34 PM	SAS System Progr...	14 KB

DATASET_METADATA file contains the data information, such as Dataset, Description, Class, Structure, Purpose

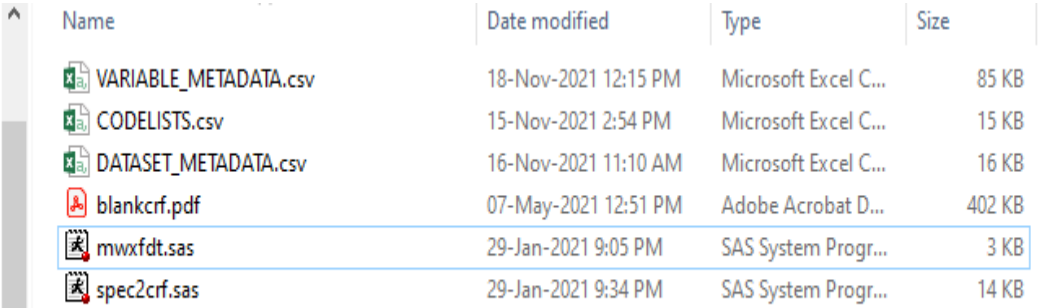
VARIABLE_METADATA file contains variable information such as Dataset, Variable, Label, Data Type

VALUE_METADATA file contains variable names and corresponding value characteristics, such as Dataset, Variable, Where Clause

Semi-automated Annotation

Step 3: Import the SDTM metadata CSV files into SAS

Copy 3 csv files, along with blank CRF, and sas programs to Unix working directory



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DATASET_METADATA.csv	16-Nov-2021 11:10 AM	Microsoft Excel C...	16 KB
blankcrf.pdf	07-May-2021 12:51 PM	Adobe Acrobat D...	402 KB
mwxfdt.sas	29-Jan-2021 9:05 PM	SAS System Progr...	3 KB
spec2crf.sas	29-Jan-2021 9:34 PM	SAS System Progr...	14 KB

Update file path if needed. Suggest to keep all working files in the same directory, then no need to update the path

Update file path as needed

```
 /*this program is to create file for CRF annotation*/
options sasautos=("./");  /*auto call SAS macro */

%let pgpath=%str(./); /*output save location*/

%let rotat=0; /*set to 0 for Portrait and 90 for Landscape orientation*/

%let tocpage=0;  /*first page number in CRF*/
/*import data pecs using LIBNAME*/

libname spec './';

%let ACROBATVERSION=11.0;
```

Semi-automated Annotation

Step 3: Import the SDTM metadata CSV files into SAS

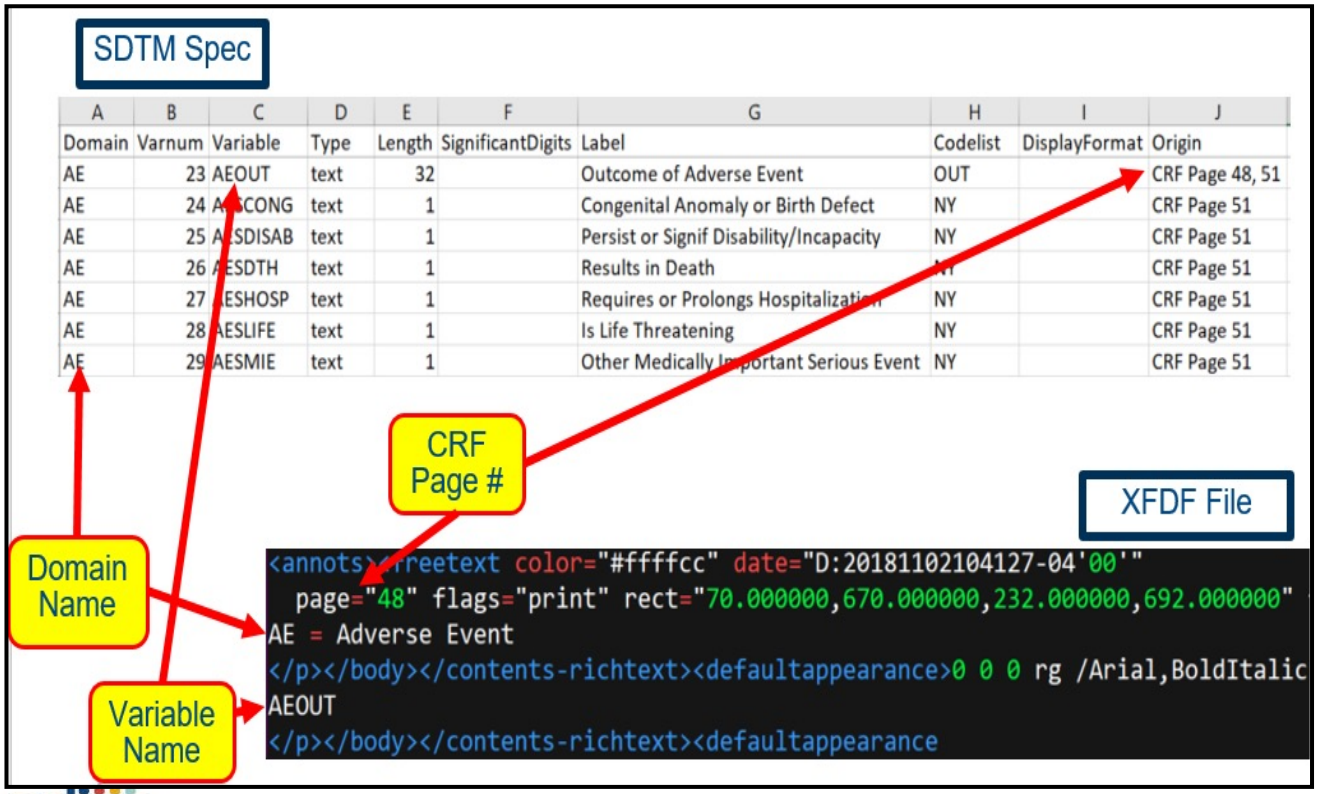
(1) %spec2crf

- Import Dataset-Level Metadata
- Import Variable-Level Metadata
- Find all dataset and domain
- Keep only records with CRF page references in Origin
- Import Value-Level Metadata
- If variable is already defined in Value Level, then it should be excluded from the Variable Level

(2)%mwxfdt: set up format and color of annotations and produce a file called anno.xfdf containing CRF annotation formatting.

Semi-automated Annotation

Step 3: Import the SDTM metadata CSV files into SAS

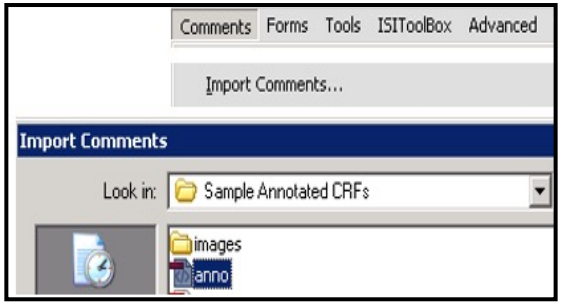


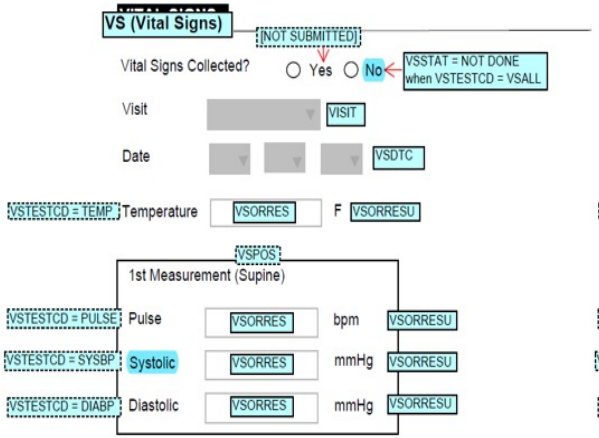
Semi-automated Annotation

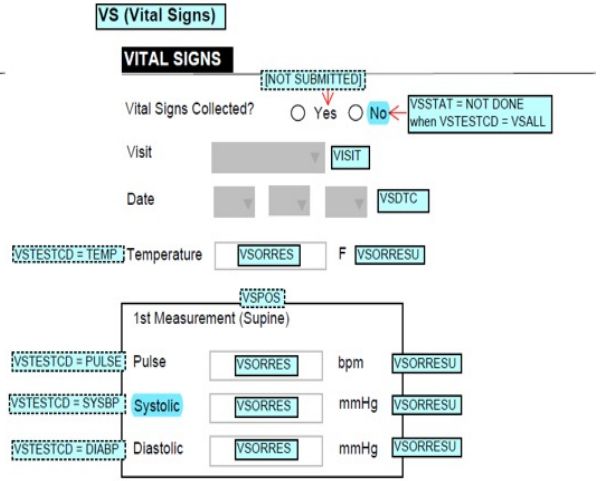
Step 4: Import annotation file

Copy anno.xfdf file

- In Adobe Acrobat, open the blank CRF file and click Comments Import → Comments → Select XFDF file produced
- Reposition the comment annotation boxes to align with CRF fields
- Save SDTM Annotated CRF file as acrf.pdf







Creating Dual Bookmarking

- Copy SDTM aCRF to the study Unix location, name as “acrf.pdf”
- Copy extract_forms.sas and makebookmark.sas
- Manually create CSV file (forms.csv) to contain all forms with associated pages and study scheduled visits from study protocol schedule map as matrix, add unscheduled visit after other visit columns. At the end, add “RUNNING LOGS” as last column.
- Semi-auto create CSV file (forms.csv)
  - Run Unix command to create forms.csv “pdftotext –raw –layout acrf.pdf forms.csv”
  - modify and run “extract_forms.sas” to produce CSV holding all form names and pages (study specific, need to review by each programmer)
- Modify and run “makebookmarks.sas” to create dual bookmarking CSV file (acrf.csv) holding all bookmark attributes
- Insert into SDTM aCRF the bookmark attributes from CSV

Creating Dual Bookmarking

Step 1: What is dual bookmarking

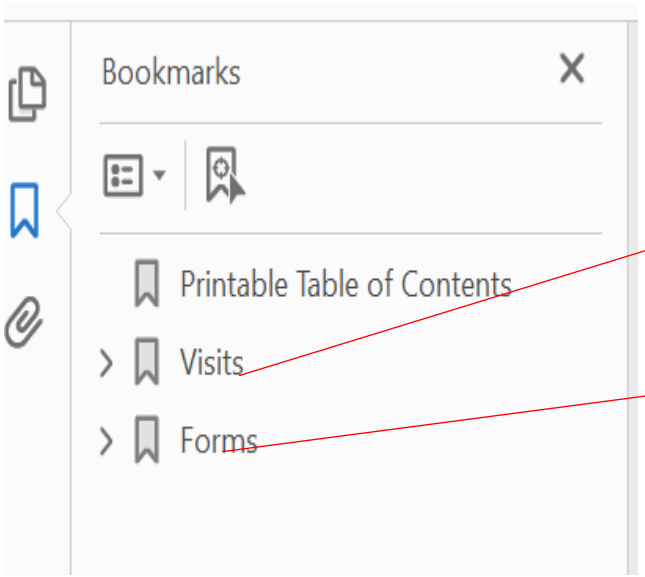
Annotated CRFs included in the eCTD should be bookmarked via dual bookmarking:
(1) bookmarks by chronology and
(2) bookmarks by CRF topics or forms.
(The terms "topics" and "forms" refer to the content of the CRF, not the SDTM domain.)
The purpose of dual bookmarking is to enhance the reviewer's ability to navigate through the unique CRFs either by chronology or by CRF topic.

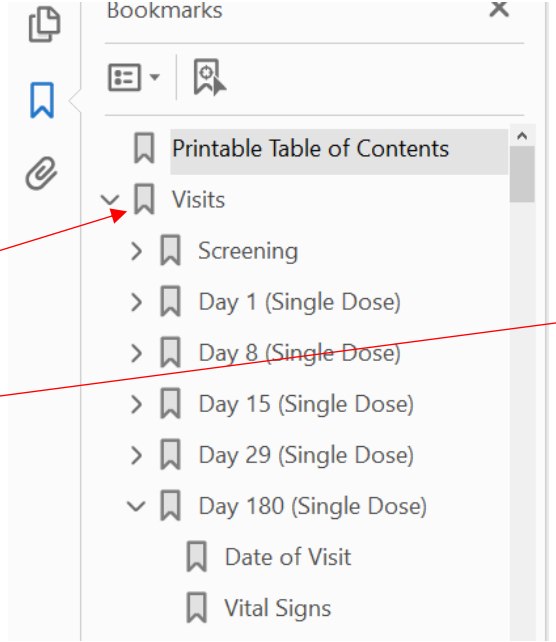
- Bookmarks by chronology should be ordered according to the study schedule of activities (SOA).
  - Pages that are independent of visits (e.g., Adverse Events) should be presented last, under a "Running Logs" bookmark.
  - Within each chronological bookmark, topic bookmarks should appear in the order that they appear in the annotated CRF.

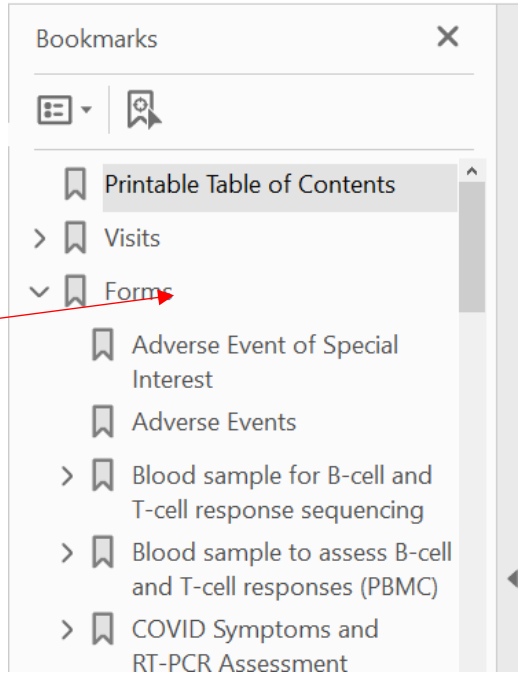
- Bookmarks by topics can be ordered alphabetically, as is done in the SDTM-MSG sample submission package, or sponsors may choose to list the forms in the order in which they appear in the CRF.
  - Within each topic bookmarks should be ordered chronologically according to the SoA schedule.
  - For SDTM-MSG v1.0, the aCRF example showed "Domains" as the top level for these bookmarks, but SDTM-MSG v2.0 has changed that to "Forms," because "Domains" implies SDTM domains.

Creating Dual Bookmarking

Step 1: What is dual bookmarking







Creating Dual Bookmarking

Step 2: Prepare bookmark csv file (forms.csv)

Method 1: From slide 25, get dataset forms which include form name and page number
Method 2: Follow SoA from protocol to manually create the template including form name and page number
Follow SoA to add Visits and the selected forms to be done on that visit, add "Running Records" at the end

Table 1 SCHEDULE OF ACTIVITIES (SoA)

	Screening [a]	Blind phase If a subject meets the eligibility at V5/ QRV, the subject will move forward to the open-label phase						Open-label phase If a subject meets the eligibility at V5/QRV, the subject will move forward to the next treatment phase						Completion visit
		Part 1					Eligibility evaluation [b]	Part 2/Part 3/ Part 4					Eligibility evaluation [b]	
Visit	**SV**	**V1 (Day 1)**	**V2**	**V3**	**V4**	**V5 [c] (Eligibility evaluation)**	**QRV**	**V1**	**V2**	**V3**	**V4**	**V5 [d] (Eligibility evaluation)**	**QRV**	**Final Visit**
Time from initial injection (Day 1) (Weeks)	—	0	2	4	6	12	Allowable Week 16 to 36 [e]	—	—	—	—	—	Allowable Week 24 to 36 [e]	48/ Withdrawal
Time from injection day in each treatment phase (Weeks)	—	0	2	4	6	12	16/ 20/ 24/ 28/ 32/ 36	0	2	4	6	12	16/ 20/ 24	-

	form	page
1	Subject Identification	1
2	Date of Visit	2
3	Screening Date of Visit	3
4	Unscheduled Visit	4
5	Demography	5

Save file as forms.csv

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA
1	Form	Page	SCREENIN	PERIOD 1	PERIOD 1	PERIOD 1	PERIOD 1	PERIOD 1	PERIOD 1	PERIOD 1	PERIOD 2	PERIOD 2	PERIOD 2	PERIOD 2	PERIOD 2	PERIOD 2	PERIOD 3	PERIOD 3	PERIOD 3	PERIOD 3	PERIOD 3	PERIOD 4	PERIOD 4	PERIOD 4	PERIOD 4	FINAL VIS	RUNNING LOGS		
2	INFORM S	41	Y																								
3	INFORM E	40	Y																								
4	DATE OF V	22		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
5	SUBJECT II	123		2																							
6	RESCREEN	104		3																							
7	DEMOGRA	32		4																							
8	ELIGIBILIT	37		5	2																						
9	SCREEN FA	109		6																							
10	INVESTIGA	43		7	4																						
11	MEDICAL (	56		8																							

Creating Dual Bookmarking

Step 3: Run makebookmark.sas on Unix to get acrf.csv

Copy makebookmark.sas, acrf.csv and CRF to Unix working directory. *%by_visit* and *%by_form* are the 2 main steps in makebookmark.sas.

```
%let indir  = ..;
%let infile = forms.csv;
%let outdir= ..;
%let outfile =acrf.csv;
%let acrf = ../acrf.pdf;

%make_bookmark(indir = &indir, infile=&infile, outdir=&outdir, outfile=&outfile, acrf=&acrf);
```

Creating Dual Bookmarking

Step 3: Run makebookmark.sas on Unix to get acrf.csv

acrf_bookmark.csv

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	
1	FILE NAME	TYPE	INDENT//	TITLE//TEXT	ACTION	MAGNIFIC	DEST. PG.	DEST. FILE	ZOOM	DEST RECT	DEST RECT	DEST RECT	DEST RECT	LEFT	RIGHT	TOP	BO
2	M:\project\readpdf\bookmark\blanl	BOOKMARI	1	Visits	Goto_Vie	FIT_WIDTI	2		0	0	0	0	605	N/A	N/A	N/A	N/
3	M:\project\readpdf\bookmark\blanl	BOOKMARI	1.1	SCREENING	Goto_Vie	FIT_WIDTI	2		0	0	0	0	605	N/A	N/A	N/A	N/
4	M:\project\readpdf\bookmark\blanl	BOOKMARI	1.1.1	12-LEAD ECG	Goto_Vie	FIT_WIDTI	2		0	0	0	0	605	N/A	N/A	N/A	N/
5	M:\project\readpdf\bookmark\blanl	BOOKMARI	1.1.2	ARM TO BE INJECTED/EVALUATED	Goto_Vie	FIT_WIDTI	4		0	0	0	0	605	N/A	N/A	N/A	N/
6	M:\project\readpdf\bookmark\blanl	BOOKMARI	1.1.3	DATE OF VISIT/ASSESSMENT	Goto_Vie	FIT_WIDTI	22		0	0	0	0	605	N/A	N/A	N/A	N/

The level of each bookmark

The form name

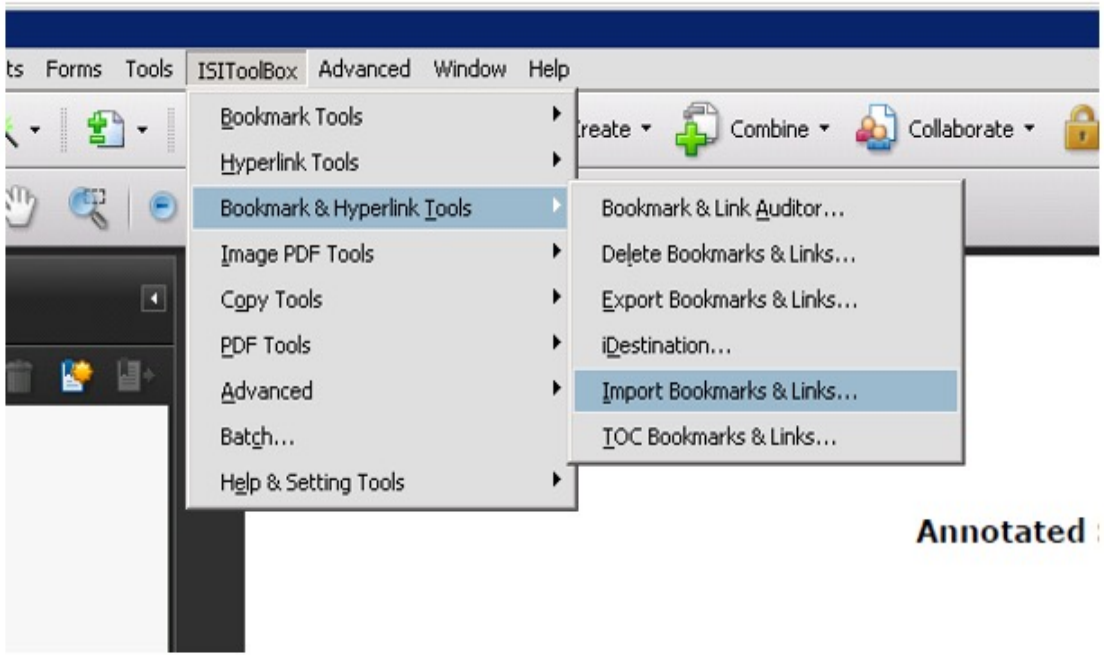
The page number of each form

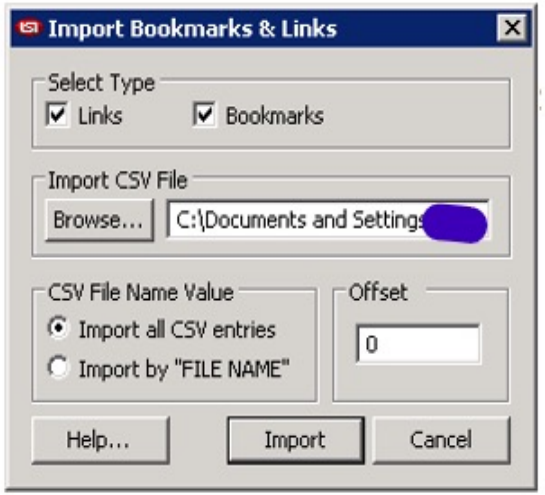
The location of destination

Creating Dual Bookmarking

Step 4: Insert into SDTM aCRF the bookmark attributes from CSV

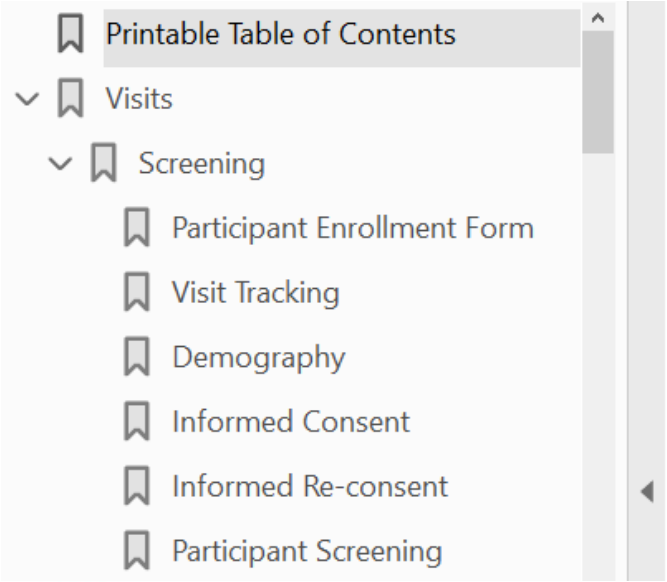
In Adobe Acrobat, open annotation CRF
After import the bookmark (acrf.csv), need to review and test the links





Creating Table of Contents

- From SDTM-MSG-V2.0, a printable TOC is requested to be included at the beginning of the annotated CRF.
- The entries in the TOC should be hyperlinked to the respective CRF page, as is done with the corresponding bookmarks.



Creating Table of Contents

The summary of the TOC procedure:

- Generate acrf.csv from dual bookmarking process and save to the study Unix location
- Copy makeacrftoc.sas from to Unix working directory
- This program generates 2 files
  - toc.doc, the table of contents in word format
  - acrf_toc.csv, the updated dual bookmarking csv file
- Update file path in the programs

Creating Table of Contents

Step 1: Prepare toc.doc and update dual bookmark acrf.csv page number

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	FILE NAM	TYPE	INDENT//	TITLE//TE	ACTION	MAGNIFIC	DEST. PG.	DEST. FILE	ZOOM	DEST RECT	DEST RECT	DEST RECT	DEST RECT	LEFT	RIGHT	TOP	BOTT
2	acrf.pdf	BOOKMARK	1	Visits	Goto_Vie	FIT_WIDTI	2		0	0	0	0	792	N/A	N/A	N/A	N/A
3	acrf.pdf	BOOKMARK	1.1	Screening	Goto_Vie	FIT_WIDTI	2		0	0	0	0	792	N/A	N/A	N/A	N/A
4	acrf.pdf	BOOKMARK	1.1.1	Participan	Goto_Vie	FIT_WIDTI	2		0	0	0	0	792	N/A	N/A	N/A	N/A
5	acrf.pdf	BOOKMARK	1.1.2	Visit Track	Goto_Vie	FIT_WIDTI	3		0	0	0	0	792	N/A	N/A	N/A	N/A
6	acrf.pdf	BOOKMARK	1.1.3	Demograp	Goto_Vie	FIT_WIDTI	4		0	0	0	0	792	N/A	N/A	N/A	N/A
7	acrf.pdf	BOOKMARK	1.1.4	Informed	Goto_Vie	FIT_WIDTI	6		0	0	0	0	792	N/A	N/A	N/A	N/A

acrf.csv

Table of Contents

toc.doc

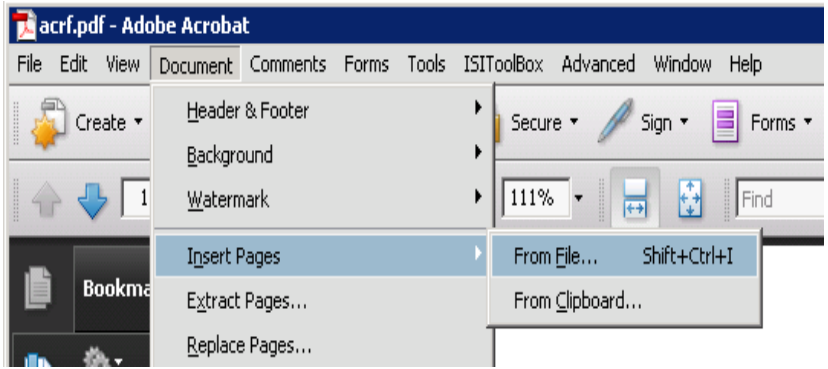
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	FILE NAM	TYPE	INDENT//	TITLE//TE	ACTION	MAGNIFIC	DEST. PG.	DEST. FILE	ZOOM	DEST RECT	DEST RECT	DEST RECT	DEST RECT	LEFT	RIGHT	TOP	BOTTOM
2	acrf.pdf	BOOKMAF	1	Printable	Goto_Vie	FIT_WIDTI	2		0	0	0	0	792	N/A	N/A	N/A	N/A
3	acrf.pdf	BOOKMAF	1	Visits	Goto_Vie	FIT_WIDTI	15		0	0	0	0	792	N/A	N/A	N/A	N/A
4	acrf.pdf	BOOKMAF	1.1	Screening	Goto_Vie	FIT_WIDTI	15		0	0	0	0	792	N/A	N/A	N/A	N/A
5	acrf.pdf	BOOKMAF	1.1.1	Participan	Goto_Vie	FIT_WIDTI	15		0	0	0	0	792	N/A	N/A	N/A	N/A
6	acrf.pdf	BOOKMAF	1.1.2	Visit Track	Goto_Vie	FIT_WIDTI	16		0	0	0	0	792	N/A	N/A	N/A	N/A
7	acrf.pdf	BOOKMAF	1.1.3	Demograp	Goto_Vie	FIT_WIDTI	17		0	0	0	0	792	N/A	N/A	N/A	N/A

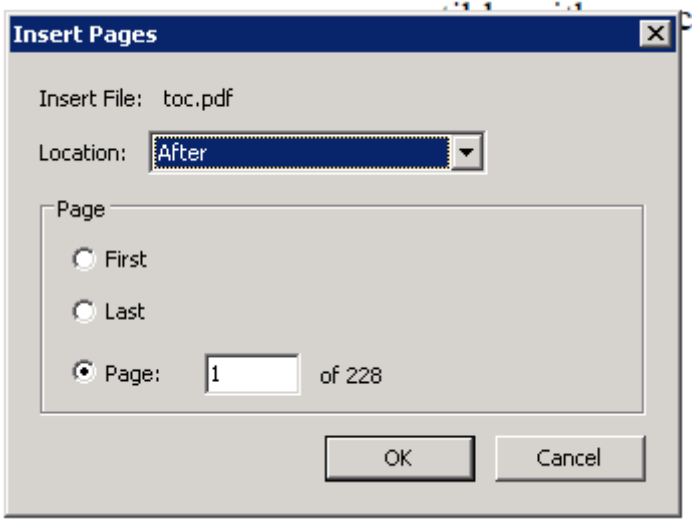
acrf_toc.csv

Creating Table of Contents

Step 2: Update acrf.pdf

- Open toc.doc in word, save as toc.pdf
- In Adobe Acrobat, open annotation CRF, append the toc.pdf at the beginning. If there is cover page of the annotation CRF, then insert toc.pdf after the cover page.

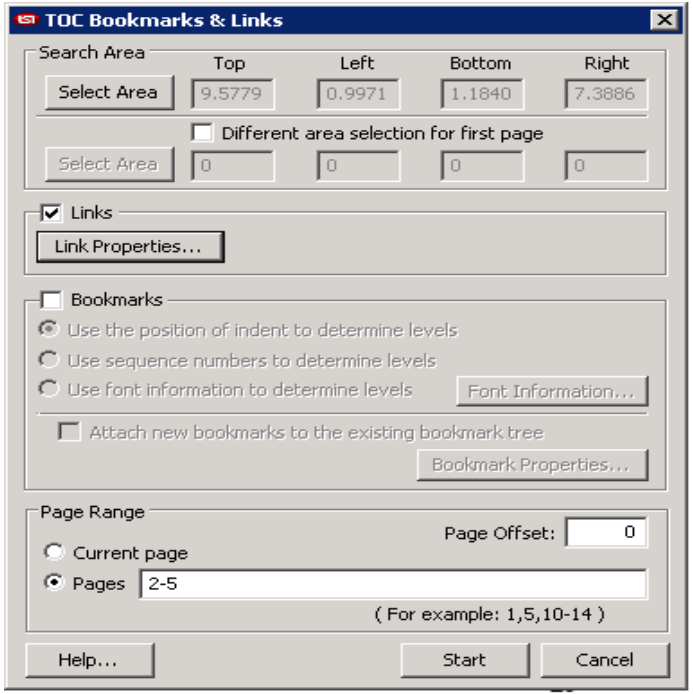




Creating Table of Contents

Step 2: Update acrf.pdf

- Set up TOC bookmarks and links
- Go to ISIToolBox - > Bookmark & Hyperlink Tools -> TOC Bookmarks & Links
- Set up the Link Properties, and TOC page ranges, you may need to setup selected area



Creating Table of Contents

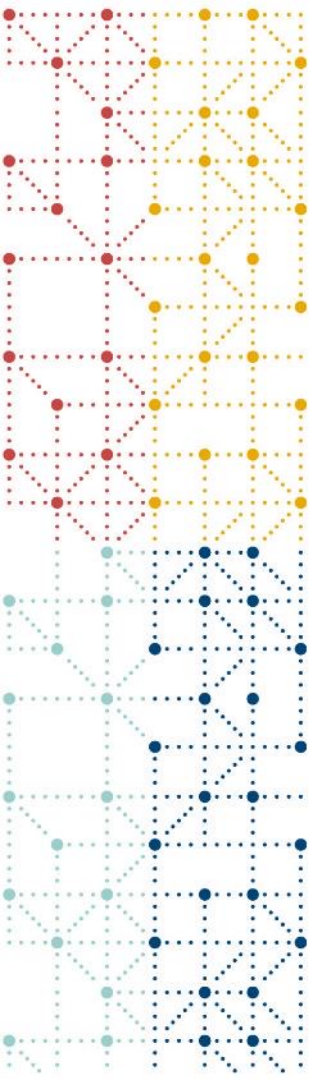
Step 3: Update dual bookmark acrf_toc.csv

- Since we insert TOC file which makes all page numbers shift, we need to load acrf_toc.csv file to update dual bookmarking, similar to what we did in slide 42
- After updating, please check the link from bookmarking and TOC

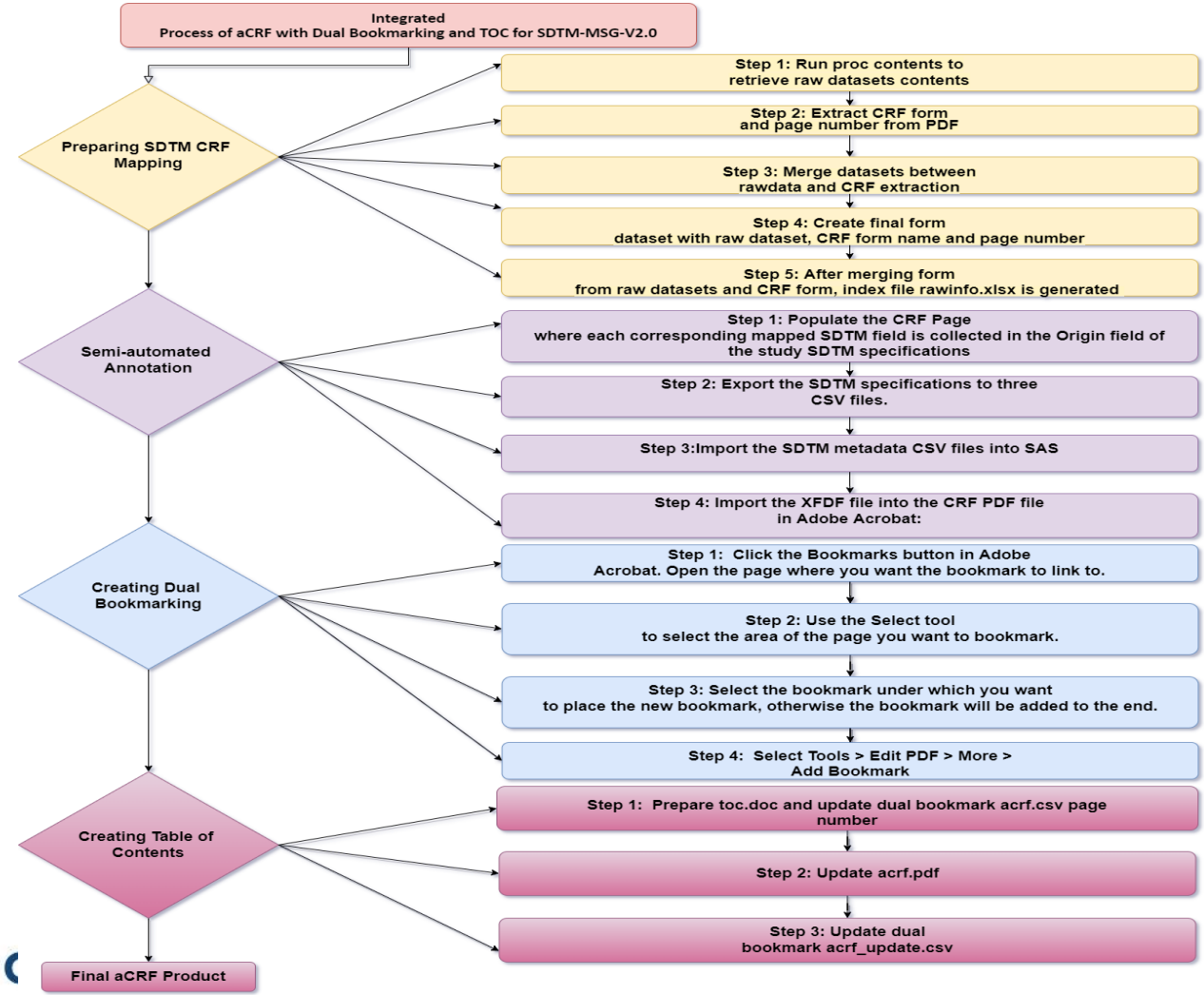
Creating Table of Contents

Step 4: Update acrf page on define spec

- Copy updatedefine.sas to Unix working directory.
- Copy define specification sheet Variables as Variables.csv and sheet ValueLevel as ValueLevel.csv and save to the same location on Unix
- Run updatedefine.sas, it will update CRF page number column for both files.
- Then save these 2 files back to define spec



Summary


Integrated
Process of aCRF with Dual Bookmarking and TOC for SDTM-MSG-V2.0
Preparing SDTM CRF Mapping
Step 1: Run proc contents to retrieve raw datasets contents
Step 2: Extract CRF form and page number from PDF
Step 3: Merge datasets between rawdata and CRF extraction
Step 4: Create final form dataset with raw dataset, CRF form name and page number
Step 5: After merging form from raw datasets and CRF form, index file rawinfo.xlsx is generated
Semi-automated Annotation
Step 1: Populate the CRF Page where each corresponding mapped SDTM field is collected in the Origin field of the study SDTM specifications
Step 2: Export the SDTM specifications to three CSV files.
Step 3:Import the SDTM metadata CSV files into SAS
Step 4: Import the XFDF file into the CRF PDF file in Adobe Acrobat:
Creating Dual Bookmarking
Step 1: Click the Bookmarks button in Adobe Acrobat. Open the page where you want the bookmark to link to.
Step 2: Use the Select tool to select the area of the page you want to bookmark.
Step 3: Select the bookmark under which you want to place the new bookmark, otherwise the bookmark will be added to the end.
Step 4: Select Tools > Edit PDF > More > Add Bookmark
Creating Table of Contents
Step 1: Prepare toc.doc and update dual bookmark acrf.csv page number
Step 2: Update acrf.pdf
Step 3: Update dual bookmark acrf_update.csv
Final aCRF Product

REFERENCES

12 ANNOTATING CRFS Oracle® Clinical Creating a Study Release 4.6.2 E18820-01 Available at: https://docs.oracle.com/cd/E22982_01/index.htm

Developing annotated CRF: SAS, Excel and patience as your friends Ilias Pyrnokokis, OCS Consulting B.V., 's-Hertogenbosch, The Netherlands PhUSE 2015 PP29 Available at: https://www.lexjansen.com/phuse/2015/pp/PP29.pdf

STUDY DATA TECHNICAL CONFORMANCE GUIDE Available at: https://www.fda.gov/media/131872/download

CDISC Study Data Tabulation Model Metadata Submission Guidelines v2.0 (SDTM-MSG) Available at: https://www.cdisc.org/standards/foundational/sdtm/sdtm-metadata-submission-guidelines-v2-0

U.S. Department of Health and Human Services Food and Drug Administration Study Data Technical Conformance Guide Technical Specifications Document Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-data-technical-conformance-guide-technical-specifications-document

Portable Document Format (PDF) Specifications, Technical Specifications Document Available at: https://www.fda.gov/media/76797/download

ACKNOWLEDGMENTS

We would like to express our sincere gratitude to our manager Weijie, Yang for the support of our paper.

Thank You!

Sample Questions

- What documents are needed for the whole process?
- AE and CM are not collected by visit, which level/hierarchy should they belong to?
- You mentioned many SAS macros. Are the whole progress completed by one integrated macro or separated macros?