



Creation of SDTM Annotated CRFs

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- Background
- Methodology
- CRF Annotation Tool
- Demo
- Notes

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Background

Why Do SDTM Annotations?

- SDTM annotated CRFs is one of the key CDISC format submission deliverables
- This is a blank CRF annotations that document the location of the data with the corresponding names of the datasets and the names of those variables included in the submitted SDTM datasets
- Annotations are meant to help the FDA reviewer find the origin of data variables included in the submitted SDTM datasets
- **Annotations should reflect the data submitted within the SDTM** and shouldn't include annotations for any Operational or Derived data
- Annotations should be text-based and searchable using standard PDF viewers
- There are specific guidelines published by CDISC for annotations. The **SDTM Metadata Submission Guidelines** should be used for additional information on SDTM annotated CRFs

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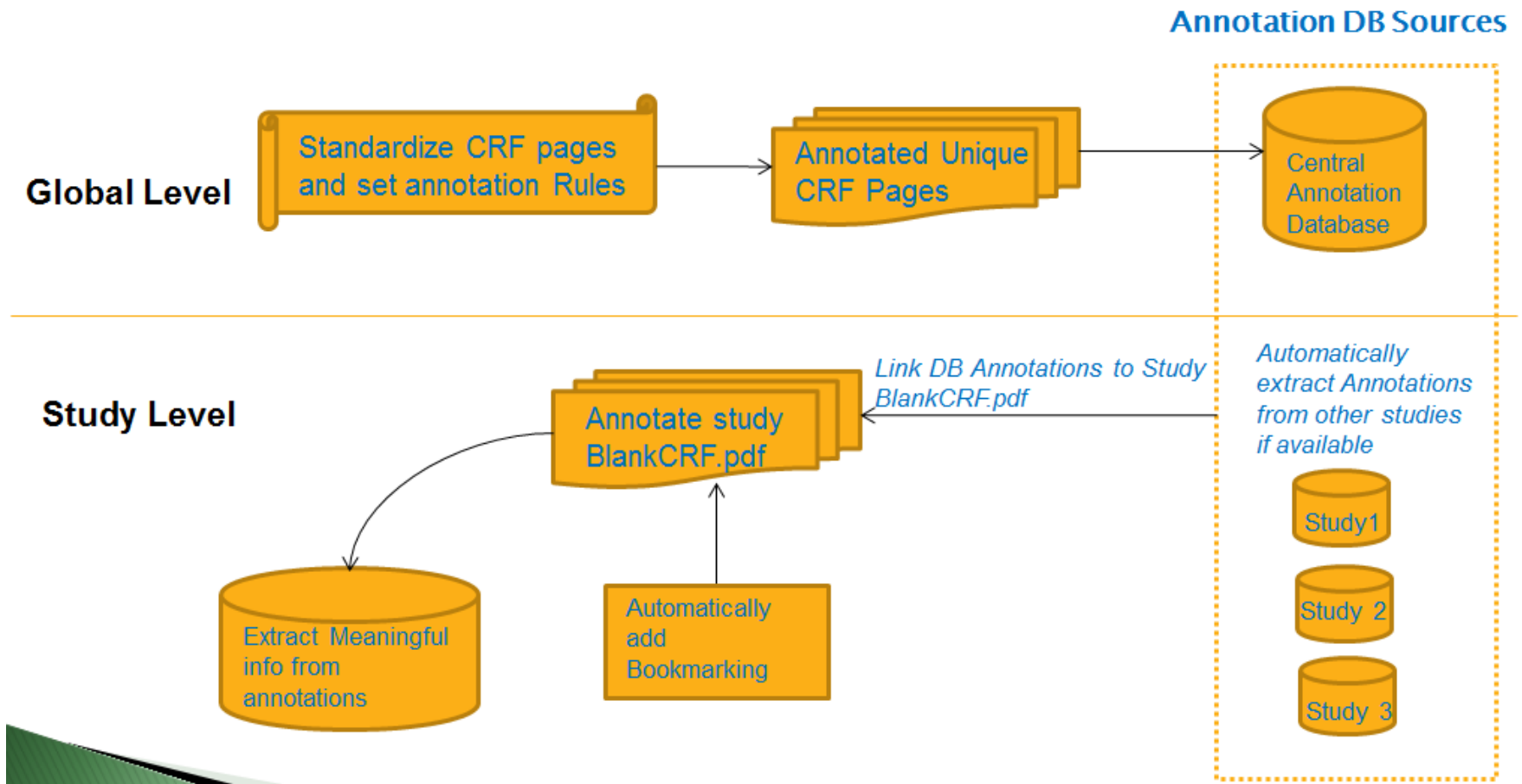
CRF Annotation Tool

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Process Flow



Methodology

Overview

- For all the global CRF pages, a **Central Annotation Database** has been developed
- For study specific CRF pages, a **Secondary Annotation Database** could be developed
- Extract **unique CRF pages** from the study blank CRF case book and specify the CRF IDs/Page No in a Excel spreadsheet for adding bookmarking
- Automatically create a **FDF file** specific to the study CRFs using the corresponding annotations from Central/Secondary Annotation Database and CRF IDs/Page No specification in Excel spreadsheet
- These comments in the FDF file can be directly imported to study blank CRFs using Adobe Acrobat software

Methodology

FDF File

- FDF stands for "Forms Data Format". FDF is a file format for representing form data and annotations that are contained in a PDF form

```
%FDF-1.2
%ããİÓ
)1 0 obj
<</FDF<</Annots[2 0 R 3 0 R 4 0 R 5 0 R 6 0 R 7 0 R 8 0 R 9 0 R 10 0 R
11 0 R 12 0 R 13 0 R 14 0 R 15 0 R 16 0 R 17 0 R 18 0 R 19 0 R 20 0 R
21 0 R 22 0 R 23 0 R 24 0 R 25 0 R 26 0 R 27 0 R 28 0 R 29 0 R 30 0 R
31 0 R 32 0 R 33 0 R 34 0 R 35 0 R 36 0 R 37 0 R 38 0 R 39 0 R 40 0 R
41 0 R 42 0 R 43 0 R 44 0 R 45 0 R 46 0 R 47 0 R 48 0 R 49 0 R 50 0 R
51 0 R 52 0 R 53 0 R 54 0 R 55 0 R 56 0 R 57 0 R 58 0 R 59 0 R 60 0 R
61 0 R 62 0 R 63 0 R 64 0 R]/F(/view/yangyie_view/CSCRTRUS/CSCRTRUS0016/
report/pkpd/pgm_02/aCRF_Study1_Demo.pdf)/ID[<
47BB8C7CE6CC1742A478E693CD1DBA04><1E0B7AA8C5B11D489645F6A43EB0AB4E>]/UF(
/view/yangyie_view/CSCRTRUS/CSCRTRUS0016/report/pkpd/pgm_02/
aCRF_Study1_Demo.pdf)>>/Type/Catalog>>
endobj
2 0 obj
<</C[0.75 1.0 1.0]/CA 0.999451/Contents(QSCAT= COLUMBIA-SUICIDE
SEVERITY RATING SCALE - SCREENING/BASELINE)/CreationDate(D:
20121210095519Z)/DA(0 G 0.75 1 1 rg 0 Tc 0 Tw 100 Tz 0 TL 0 Ts 0 Tr /
Arial 9 Tf)/DS(font: Arial,sans-serif 9.0pt; text-align:left; color:#
BFFFFFF )/F 4/M(D:20140706153541-04'00')/NM(72fafae6-d359-48e8-adc1-
f9270e9fe220)/Page 0/Q 1/RC(<?xml version="1.0"?><body xmlns="http://
www.w3.org/1999/xhtml" xmlns:xfa="http://www.xfa.org/schema/xfa-data/1.0
/" xfa:APIVersion="Acrobat:10.1.5" xfa:spec="2.0.2" style="font-size:
8.0pt;text-align:left;color:#000000;font-weight:normal;font-style:normal
\
;font-family:Arial;font-stretch:normal"><p dir="ltr"><span style="font-
size:9.0pt">QSCAT= COLUMBIA-SUICIDE SEVERITY RATING SCALE - SCREENING/
BASELINE</span></p></body>)/Rect[404.585 436.168 778.443 452.361]/
Subtype/FreeText/T(OPA)/Type/Annot>>
endobj
```


Methodology

Unique CRF Pages

- Each unique CRF page has a unique CRF ID to identify it. It is available in the lower left corner of every CRF page in Novartis
- Page No can be found in the toolbar

 Study CAIN457A2317	ID Center No. Subject No.	ADVERSE_EVENTS Visit Name
---	------------------------------	------------------------------

Adverse Events

Please make a separate entry for:
-All new adverse events
-All adverse events which have increased severity category
-All adverse events with changes in study drug relationship
-All medical conditions present at the signing of informed consent which have worsened

Unique Event ID (derived)

Were any adverse events reported? ☐ No ☐ Yes ☐ Unknown

Adverse event term

Does AE meet the definition of an SAE? ☐ No ☐ Yes

Date SAE report submitted to Novartis
DD-MON-YYYY

Severity

Reasonable possibility that AE is related to study treatment ☐ No ☐ Yes

Start date End date
DD-MON-YYYY DD-MON-YYYY

Action taken with study treatment

Medication or therapies taken?

Outcome

AEG01

AEG01

Epoch	Summary	Document Number	Subevent#	Page Number 132
Verified ☐	Approved ☐	Locked ☐	Frozen ☐	Page Name ADVERSE EVENT
Status			Version 1	

Create ▾



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	A	B
1	CRFID ▾	PAGE ▾
2	AEFA4_1	1
3	AEFA4_2	2
4	AEFA4_3	3
5	AEG01	4
6	CEC02\$1	5

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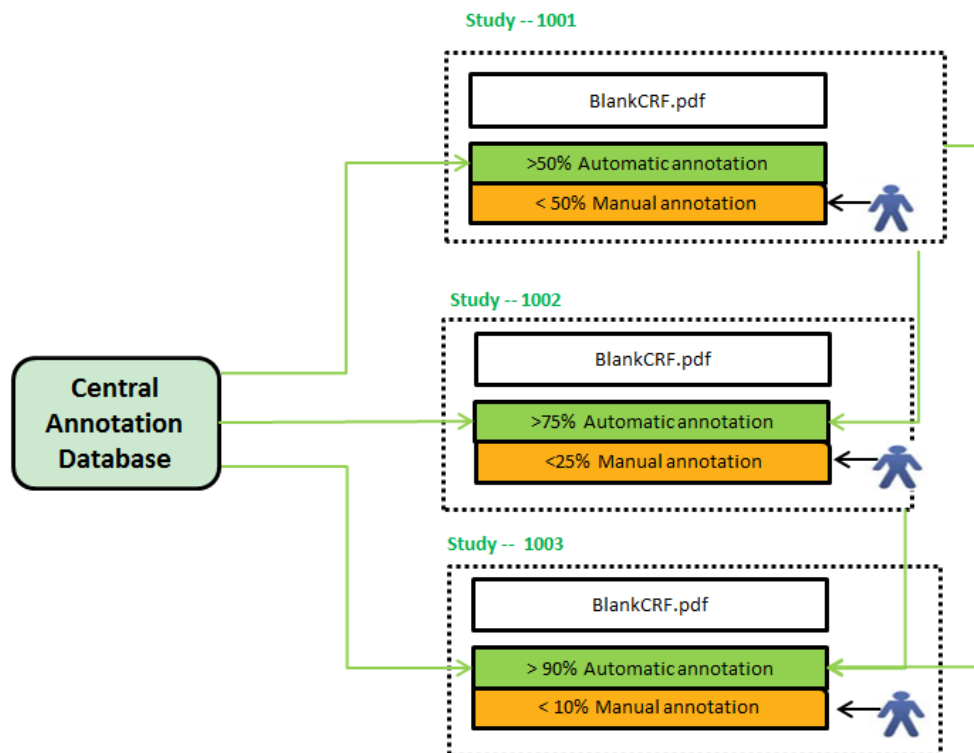
Demo

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CRF Annotation Tool

Overview

- To streamline study level annotations, a SAS based tool has been developed to write SDTM annotations onto blank CRFs
- This would help reducing time and resources for this task and also help maintaining consistency in SDTM across Novartis



CRF Annotation Tool

Primary Input – Central Annotation Database

- Built from already annotated global CRF pages
- Maintained in a central location --- CRF Annotation tool can use it as input directly

	comment	cord	crfid	comtype	domlvl	domain
1	RACEOR in SUPPDM	125.641 283.284 230.815 296.394	DMG02	FreeText	1	DM
2	RACESY in SUPPDM	125.795 257.753 225.384 270.863	DMG02	FreeText	1	DM
3	AGEU	372.227 383.174 401.703 395.184	DMG02	FreeText	1	DM
4	SEX	398.805 320.704 421.53 334.814	DMG02	FreeText	1	DM
5	BRTHDTC	383.517 429.661 472.057 442.981	DMG02	FreeText	1	DM
6	AGE	307.456 384.224 335.693 396.234	DMG02	FreeText	1	DM
7	BRTHDTC	345.794 401.775 434.334 415.095	DMG02	FreeText	1	DM
8	BRTHCL in SUPPDM	384.688 448.777 494.896 461.787	DMG02	FreeText	1	DM
9	DM = Demographics	58.3869 574.487 194.345 591.609	DMG02	FreeText	1	DM
10	ETHNICOR in SUPPDM	125.898 238.6 228.099 251.71	DMG02	FreeText	1	DM
11	STUDYID	159.985 554.563 206.077 568.163	DMG02	FreeText	1	DM
12	USUBJID	401.697 554.17 445.183 567.77	DMG02	FreeText	1	DM
13	VISIT	656.707 547.747 686.371 561.347	DMG02	FreeText	1	DM
14	SRCRFSY in SUPPSC	527.093 196.758 637.871 211.489	DMG02	FreeText	2	SC
15	SCORRES when SCTESTCD=INITCL	386.337 363.28 548.562 377.934	DMG02	FreeText	2	SC
16	SC = Subject Characteristics	10.5666 390.108 195.71 410.124	DMG02	FreeText	2	SC
17	SCORRES when SCTESTCD=SRCRF	527.422 218.31 693.821 230.32	DMG02	FreeText	2	SC
18	SCORRES when SCTESTCD=SBJINIT	387.831 340.796 560.515 355.918	DMG02	FreeText	2	SC
19	SCORRES when SCTESTCD=CHDBER	527.951 299.432 718.581 313.002	DMG02	FreeText	2	SC
20	STUDYID	159.985 554.563 206.077 568.163	FHI01	FreeText	1	SC

CRF Annotation Tool

Secondary Input(s) – Secondary Annotation Database(s)

- Functionality to re-use already annotated study level CRF pages
- Follows the same structure as Central Annotation Database
- Export annotations from each already annotated study level CRF pages to a **FDF file**
- Create each annotation database with FDF file as input --- Repeat the process for as many FDF files as possible

CRF Annotation Tool

SAS Programs

- Macro name: `extract_annotations.sas`
 - Inputs: FDF files exported from already annotated study level CRF pages
 - Output: Secondary Annotation Database(s)

- Macro name: `create_fdf_file.sas`
 - Inputs:
 - Central Annotation Database
 - Secondary Annotation Database(s) (no number limitation), if any
 - CRF IDs/Page No in a Excel spreadsheet
 - Output: study specific **FDF file** that could be imported to the study blank CRFs

- Functionality to give user the option to pick the order of preference if annotations for same CRF ID are available from multiple sources

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Input Files

Name	Size
 master_annotation.sas7bdat	499712

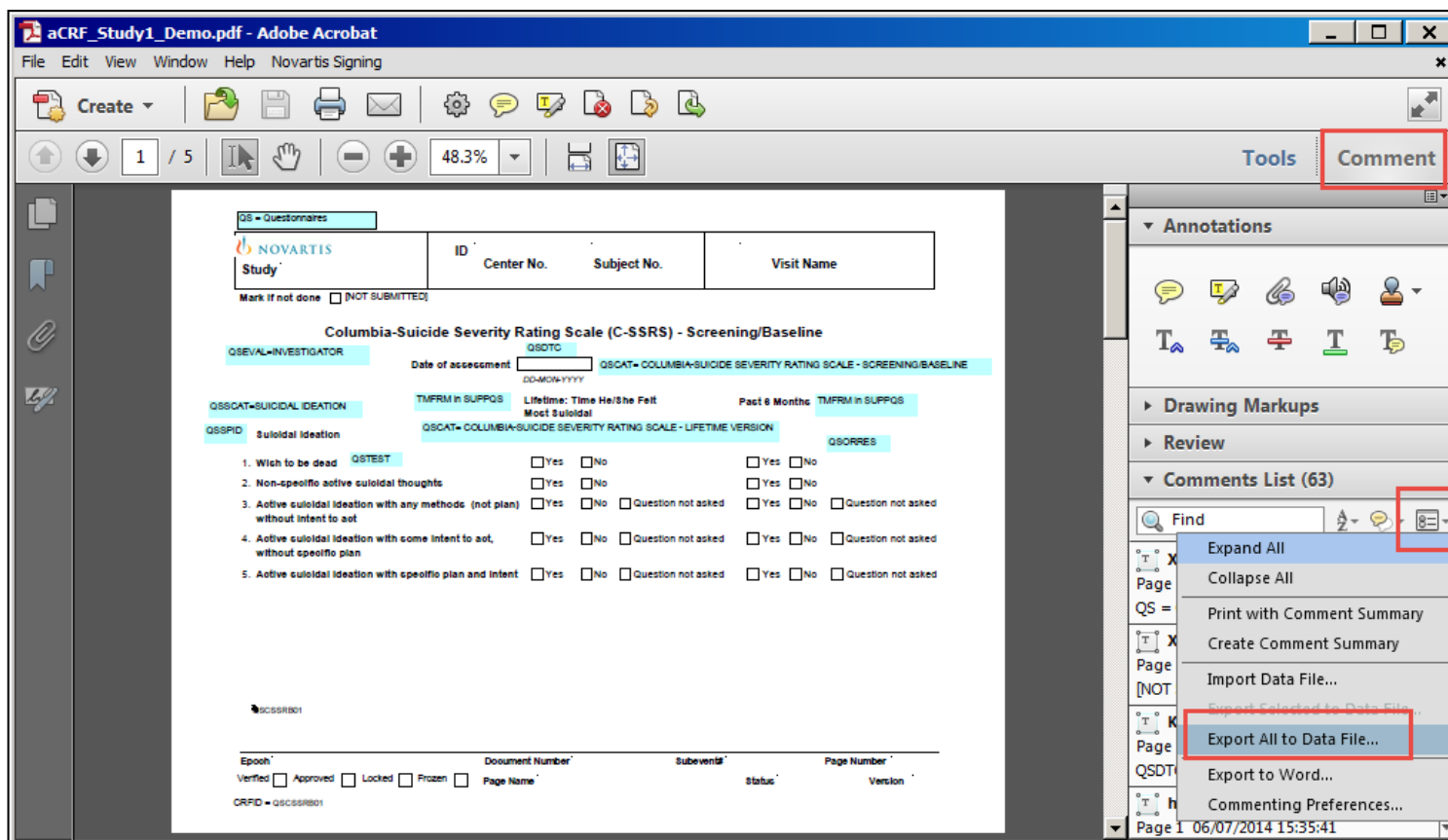
Name	Size
 BlankCRF_Study2_Demo.pdf	300317
 aCRF_Study1_Demo.pdf	1505181
 crfid_pageno.xls	31232
 extract_annotation.sas	23561
 create_fdf_file.sas	17108

- **master_annotation.sas7bdat**: Central Annotation Database
- **BlankCRF_Study2_Demo.pdf**: Blank CRFs to annotate for Study 2
- **aCRF_Study1_Demo.pdf**: Already annotated CRF pages from Study 1
- **crfid_pageno.xls**: CRF IDs/Page No specification
- **extraction_annotation.sas**: SAS program to create Secondary Annotation Database(s)
- **create_fdf_file.sas**: SAS program to create study specific FDF file

Demo

Create Secondary Annotation Database

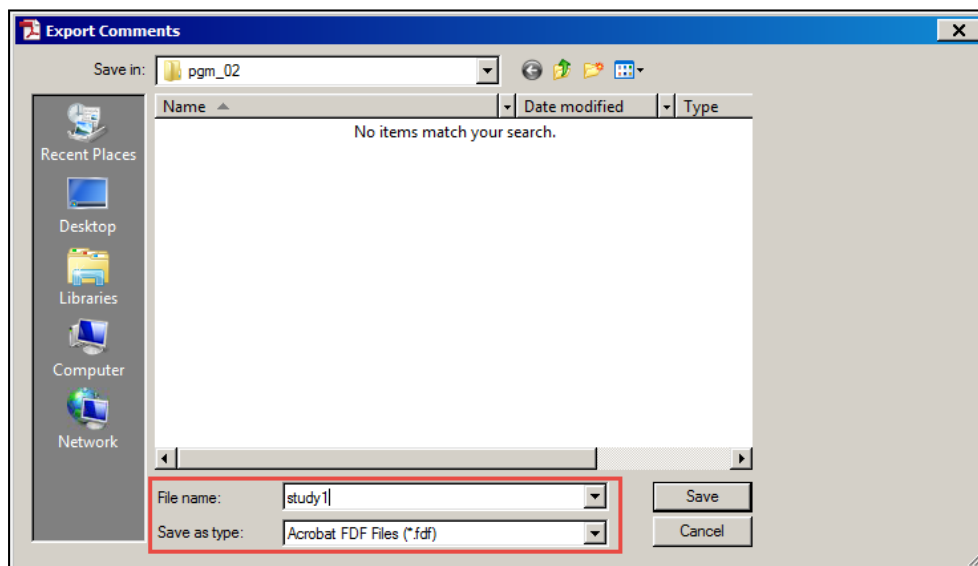
- Open aCRF_Study1_Demo.pdf -> Click on “Comments” on the top right corner of the pdf file -> Click on the tab on the right side of “Comments List” -> Click “Export All to Data File”



Demo

Create Secondary Annotation Database (Cont'd)

- Save as a FDF file named as **study1.fdf**



Name	Size
BlankCRF_Study2_Demo.pdf	300317
aCRF_Study1_Demo.pdf	1505181
crfid_pageno.xls	31232
extract_annotation.sas	23561
create_fdf_file.sas	17108
study1.fdf	48074

- Call macro %extract_annotation with study1.fdf as input to create Secondary Annotation Database named as **study1.sas7bdat**

```
%extract_annotation(FDFLIB      = 1,/*util*/  
                   FDFNAME      = study1.fdf,/*AnnotatedCRF_Study1.fdf*/  
                   CRFID_SOURCE = ANNOTATION,  
                   INPUT_XLS    = ,/*util.crfid_pageno*/  
                   OUTDS        = 1.study1);/*util.annotations_Study1*/
```

Name	Size
BlankCRF_Study2_Demo.pdf	300317
aCRF_Study1_Demo.pdf	1505181
crfid_pageno.xls	31232
extract_annotation.sas	23561
create_fdf_file.sas	17108
study1.fdf	48074
study1.sas7bdat	2236416

Demo

Create Study Specific FDF File

- Call macro %create_fdf_file with master_annotation.sas7bdat, study1.sas7bdat and crfid_pageno.xls as inputs to create the FDF file for Study 2 named as **outfdf_demo2.fdf**

```
%create_fdf_file(annotation_database = fdfappr.master_annotation|1.study1  
                , input_xls         = 1.crfid_pageno  
                , output_fdf        = 1.outfdf_demo2);|
```

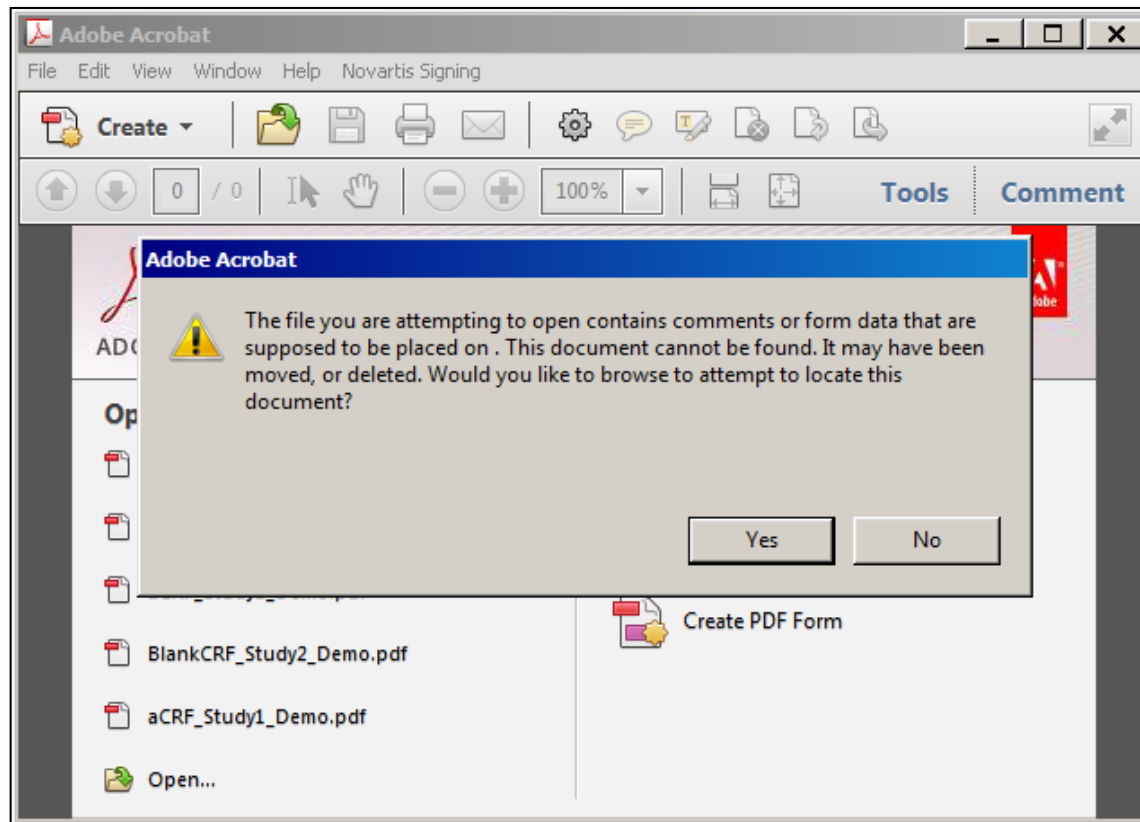
Name	Size
 master_annotation.sas7bdat	499712

Name	Size
 BlankCRF_Study2_Demo.pdf	300317
 aCRF_Study1_Demo.pdf	1505181
 crfid_pageno.xls	31232
 extract_annotation.sas	23561
 create_fdf_file.sas	17108
 study1.fdf	48074
 study1.sas7bdat	2236416
 outfdf_demo2.fdf	58788

Demo

Import Annotations into Study Blank CRFs

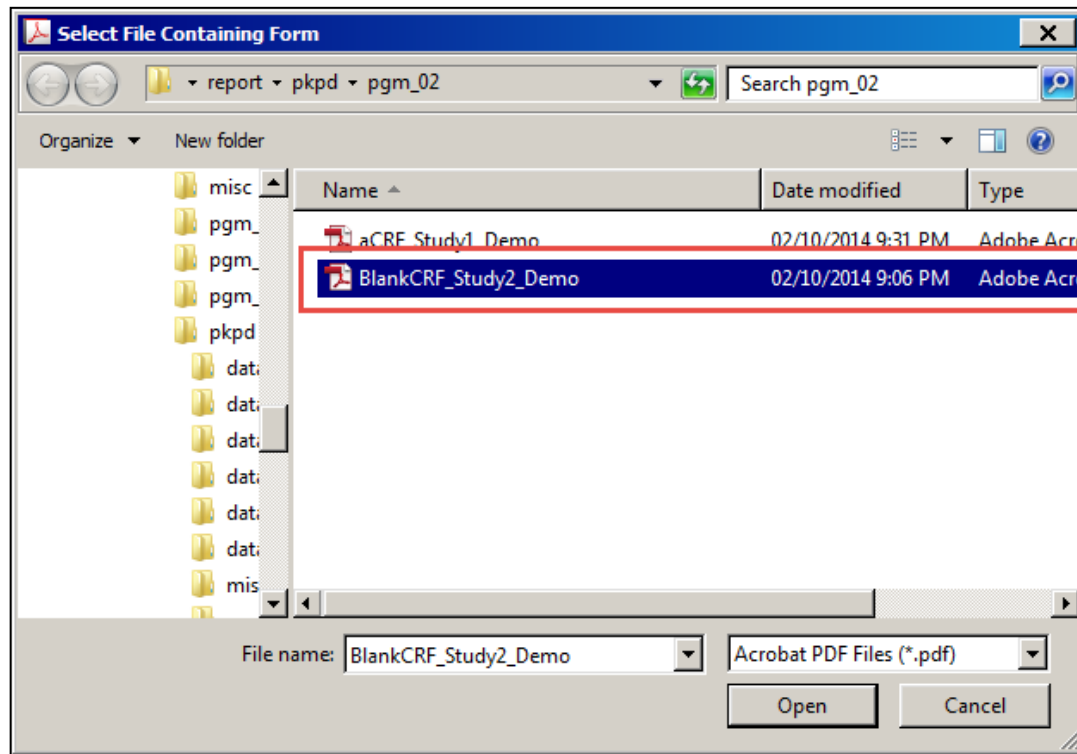
- Open outfdf_demo2.fdf -> Click on “Yes”



Demo

Import Annotations into Study Blank CRFs (Cont'd)

- Select the blank CRFs file BlankCRF_Study2_Demo.pdf -> Click on “Open”



Demo

Import Annotations into Study Blank CRFs (Cont'd)

- Annotations are successfully imported -> Save and quit this file

BlankCRF_Study2_Demo.pdf - Adobe Acrobat

File Edit View Window Help Novartis Signing

Create

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Tools Comment

Q5 = Questionnaires

NOVARTIS Study

ID Center No. Subject No. Visit Name

Mark if not done ☐ [NOT SUBMITTED]

Columbia-Suicide Severity Rating Scale (C-SSRS) - Screening/Baseline

QSEVAL=INVESTIGATOR QSDTC

Date of assessment DD-MON-YYYY

QSCAT= COLUMBIA-SUICIDE SEVERITY RATING SCALE - SCREENING/BASELINE

QSSCAT=SUICIDAL IDEATION TMFRM in SUPPOS Lifetime: Time He/She Felt Most Suicidal Past 6 Months TMFRM in SUPPOS

QSSPID Suicidal Ideation QSCAT= COLUMBIA-SUICIDE SEVERITY RATING SCALE - LIFETIME VERSION QSORRES

1. Wish to be dead QSTEST ☐ Yes ☐ No ☐ Yes ☐ No

2. Non-specific active suicidal thoughts ☐ Yes ☐ No ☐ Yes ☐ No

3. Active suicidal ideation with any methods (not plan) without intent to act ☐ Yes ☐ No ☐ Question not asked ☐ Yes ☐ No ☐ Question not asked

4. Active suicidal ideation with some intent to act, without specific plan ☐ Yes ☐ No ☐ Question not asked ☐ Yes ☐ No ☐ Question not asked

5. Active suicidal ideation with specific plan and intent ☐ Yes ☐ No ☐ Question not asked ☐ Yes ☐ No ☐ Question not asked

SCSSRB01

Everything below the line: [NOT SUBMITTED]

Epoch Document Number Subevent# Page Number

Verified ☐ Approved ☐ Locked ☐ Frozen ☐ Page Name Status Version

CRFID=QSCSSRB01

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Notes

- When data are recorded on the CRF but are not submitted, the CRF should be annotated with the text “**NOT SUBMITTED**”. There should be an explanation in the **Study Data Reviewer's Guide** stating why data have not been submitted
- The annotated CRFs should be provided as a PDF with the file name “acrf.pdf”
- Bookmarking should be done in 2 ways (**dual bookmarking**)
 - Bookmarks by visits/time points in the study, should be ordered chronologically according to the study time and events with study level bookmarks (e.g. Adverse Events) presented last. Within each visit, topic bookmarks should appear in order that they appear in the annotated CRF
 - Bookmarks by CRF topics, should be ordered alphabetically. Within each topic all applicable time points should be ordered according to the study time and event schedule.
- SDTM domains do not necessarily have a one-to-one relationship with the CRF pages. E.g., both DM and SC are collected on the Demography page, while SC data are collected from both the Enrollment page and the Demography page. Hence dual bookmarking helps reviewer to navigate either by time points or by CRF topics

Questions

