

Best Practices for aCRF

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Author Bio

I'm a Product Manager at Pinnacle 21

- ▶ MS Epidemiology from The Ohio State University
- ▶ SAS Programmer
- ▶ Pinnacle 21 since 2018
- ▶ Passionate about data quality and fit-for-use assessments

+ **Caveat:** I'm not an expert on aCRF annotations and creation but I have made several SDTM aCRFs and enjoy researching the topic

Agenda

I'm a Product Manager at Pinnacle 21

- ▶ aCRF Overview
- ▶ Technical Requirements
- ▶ Suggested & Additional Guidance
- ▶ Methods of Creation
- ▶ Verification & Validation
- ▶ Conclusion

+ **PRO TIP:** Don't forget to look for the PRO TIPS on each slide!

Overview

The annotated Case Report Form (aCRF) is a PDF document that maps the clinical data collection fields used to capture subject data (electronic or paper) to the corresponding variables or discrete variable values contained within the SDTM datasets.

The aCRF may be reviewed as a stand-alone document or in concert with other files (i.e. define.xml or reviewer's guide)

+ **PRO TIP:** Make your aCRF early in the process – suggested to be submitted to FDA with protocol

Overview

DS=Disposition	
CDISC Study CDISC01	
RANDOMIZATION	
DSTERM / DSDECOD = RANDOMIZED	
DM=Demographics	RANDNO in SUPPDM
Will the patient be randomized?	☐ Yes Enter Randomization Number
RAND in SUPPDM	Randomization Date
	MM DD YYYY
	DSSTDTC
☐ No Complete Termination	

+ PRO TIP: Don't assume examples are correct.

Technical Requirements

Any process for creating the aCRF must consider and conform to the **FDA Technical Conformance Guide**

- ▶ The name of the file is “acrf.pdf”
- ▶ The aCRF should include treatment assignment forms (when applicable) and map each variable on the CRF to the corresponding variables in the datasets.
- ▶ The aCRF should include the variable names and coding for each CRF item
- ▶ 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 relevant Reviewers Guide stating why these data have not been submitted.

+ **PRO TIP:** See details in §4.1.4.6 of the Technical Conformance Guide

Technical Requirements

Any process for creating the aCRF must consider and conform to the **FDA Portable Document PDF Specifications**

- ▶ Text should be searchable
- ▶ Any hyperlinks in the documents should be active
- ▶ Submitted PDF should not be password protected
- ▶ Use standard fonts (preferred), in a range of 9- 12 points.
- ▶ The left margin (top margin for landscape) should be at least 3/4 inch. All other margins should be at least 3/8 inch
- ▶ Include a Table of Contents with hyperlinks to bookmarked pages. Zoom settings should persist when navigating the document

+ **PRO TIP:** If you can't use standard fonts, full embed your non-standard font into the document.

Suggested Guidance

Any process for creating the aCRF should consider the **Metadata Submission Guidelines (MSG) & SDTM aCRF Guidelines by German Speaking CDISC User Group**

- ▶ The aCRF should be bookmarked in two ways – by visit and by form
- ▶ If more than one domain exists on a page, each domain annotation, and all variables, should be color-coded.
- ▶ All text in the annotations that represent variable and domain names should be capitalized.
- ▶ Each domain that is represented on a CRF page should have its own annotation on the upper left side of the CRF page with the 2-letter domain code and domain name.

+ **PRO TIP:** The annotations should not obstruct any text on the CRF page. A sponsor may choose to resize the domain annotation based on the CRF layout.

Suggested Guidance

Any process for creating the aCRF should consider the **Metadata Submission Guidelines (MSG) & SDTM aCRF Guidelines by German Speaking CDISC User Group**

- ▶ The aCRF should include additional collection documents if those data were not transcribed into the CRF (i.e. patient diaries).
- ▶ The aCRF should not have database annotations on it.
- ▶ The aCRF must be complete – it contains all final unique CRF pages/modules. It should not contain any blank pages.

+ **PRO TIP:** If additional data sources are used (i.e. patient diaries), they should be appended to the aCRF instead of submitted separately or as part of the SDRG. In this case, the origin should still be eDT. Note, this requirement is only needed if the information in the additional data source is not transcribed into the eCRF.

Suggested Guidance

Any process for creating the aCRF may consider additional guidance sourced from prior publications.

- ▶ Use conventions for annotations

Type	Annotation Pattern	Examples
Domain	[Domain Short Name] = [Domain Long Name]	AE = Adverse Events
Variable	VARNAME (when prefix is the same as domain)	AETERM
	DATASET.VARNAME (when prefix is not the same as domain)	LB.VISIT
Unsubmitted data	[NOT SUBMITTED]	[NOT SUBMITTED]

+ **PRO TIP:** Creating and implementing the use annotation conventions will make any kind of future automation much easier

Suggested Guidance

Any process for creating the aCRF may consider additional guidance sourced from prior publications.

- ▶ Use conventions for annotations

Type	Annotation Pattern	Examples
Variable & Value	VARNAME = VALUE	DSTERM = "RANDOMIZED" DSTERM/DSDECOD = "RANDOMIZED"
Supplemental QVAL	QVAL where QNAM = VALUE	SUPPDM.QVAL where QNAM = "RACE1"
Value Level (non-SUPP)	VARNAME1 where VARNAME2 = VALUE1 VARNAME1 where VARNAME2 = VALUE1 AND VARNAME3 = VALUE2	VSORRES where VSTESTCD = "SYSBP" FAORRES where FATESTCD = "ONSETDTC" and FAOBJ = "TRIAL DISEASE"

Suggested Guidance

Any process for creating the aCRF may consider additional guidance sourced from prior publications.

- ▶ When applicable, annotate the --CAT. When it is printed on the CRF, an annotation of --CAT next to the category printed on the CRF is sufficient. If not printed on the CRF, it can be annotated as --CAT = “VALUE”
- ▶ Annotate variables by listing them separately. Only combine variables that map to the same value. For example, ORRES/STRESC not ORRES/ORRESU.
- ▶ When the variables prefix doesn't match the domain's prefix, include the domain name in the annotation (for example: APDM.SREL)

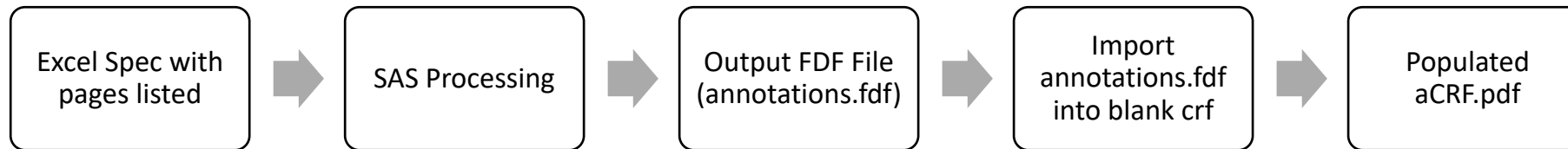
+ **PRO TIP:** Document your annotation conventions and norms for your organization

Methods to Create the aCRF

Now that you know the requirements and suggested guidance for the aCRF, pick a creation method that works for your organization.

- ▶ Semi-Automation Methods with FDF creation/import

- ▶ Typically created in-house using SAS programming



- ▶ Fully-automated solutions are emerging but few published success stories
- ▶ Don't forget to think about bookmarking and TOC when choosing a creation method

+ **PRO TIP:** At some point, you will need to make manual edits to the aCRF – ensure you have a good editor (Acrobat isn't the only solution!)

Verification & Validation of aCRF

Automation outputs are only as good as the inputs. Ensuring the quality of the aCRF is incredibly important to helping reviewers properly navigate study data.

- ▶ Validation – using a checklist
 - ▶ Check XML origin=CRF against FDF annotations file.
 - ▶ Check mapping specs against FDF annotation file
- ▶ Validation – using a checklist

+ **PRO TIP:** Parsing the text in the FDF file will be much easier if you followed annotation conventions!

Verification & Validation of aCRF

Sample aCRF Validation Checklist

- ☐ The document meets FDA technical requirements
- ☐ The document meets MSG requirements
- ☐ Each domain that is represented on the page should be listed at the top of the page
- ☐ All annotations follow the pre-defined convention syntax
- ☐ When all annotations on the page belong to the same domain, the background color should be light blue
- ☐ When annotations on the page come from multiple domains, the annotations should be color-coded by domain

Verification & Validation of aCRF

Sample aCRF Validation Checklist

- ☐ EVAL is only annotated on the CRF when collected
- ☐ Annotations do not obstruct any text on the page
- ☐ It's clear for each annotation which domain it belongs to
- ☐ All data points are annotated, [NOT SUBMITTED] is used when data are not mapped to SDTM
- ☐ When applicable, --CAT is annotated
- ☐ All annotations do not contain typos and are searchable
- ☐ Annotation text does not contain pseudo-code

Conclusion

- ▶ The aCRF is critical for FDA review but guidance from agency isn't very robust
- ▶ Guidance from CDISC and literature reviews can help
- ▶ The best documents start with the best processes

+ **PRO TIP:** Check out Qoppa Software as a cheaper alternative to Adobe Acrobat (I am not affiliated with Qoppa in any way)

| Thank You! Questions?

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