Guide

How to Automate CRF Annotations

A Best Practice Guide

CERTARA

Introduction

Case report form (CRF) annotations have been a mandatory regulatory requirement for study submission deliverables since 2016.

Annotated CRFs provide traceability by helping FDA reviewers find the origin of data variables in the submitted SDTM datasets. So, it's important that they're done properly, and that nothing is left out. Even with the regulatory guidance that's available, creating good quality, compliant annotated CRFs can seem a little overwhelming.

The good news is that there are things you can do to simplify and expedite your CRF annotations.

We've created this guide to help you better understand:

- CRF annotations and how they can be automated
- How automated annotations can be applied to your clinical trials
- How automation can help you free up time to focus on what counts: getting safe and innovative treatments to those in need faster

The technical specs

Firstly, it's useful to have an overview of exactly what the FDA expects to see when it comes to annotated CRFs.

The FDA's study data technical conformance guide section 4.1.4.6 (available on the FDA website) lays out guidance for how annotated CRFs (aCRFs) should be prepared and submitted.

We've summarized some key points from the guide below.

Submission time
aCRFs should be submitted ideally at the same time a protocol is submitted.

Format
The aCRF should be in PDF format and should have the file name 'acrf.pdf.

Treatment assignment forms
aCRFs should include treatment assignment forms if relevant, and should map each variable on the CRF to the corresponding variables in the datasets or database.

Variables
For each CRF item, include the variable names and coding.

Not submitted
When data is recorded on the CRF but is not submitted, the CRF should be annotated with the text 'NOT SUBMITTED.' Include an explanation in the relevant reviewer's guide stating why these have not been submitted.

CERTARA

Format matters

Because the annotated CRF is submitted as a PDF, it's also subject to the specifications in the FDA's portable document format (PDF) specifications guide (available on the FDA website).

See below summary of some key requirements. Note, this list is not exhaustive, so you should review the specification guide for a full list of technical requirements, including guidelines for page layout and document navigation.

- Submitted PDF files should be in PDF versions 1.4 through 1.7, PDF/A-1 and PDF/A-2 and readable in Adobe Acrobat
- Documents should not be password protected
- Only standard fonts should be used at 9-12pt, and any nonstandard fonts should be fully embedded. You can see a full list of standard fonts in the PDF download
- It's recommended that text should be black, but blue is permitted for hyperlinks
- The PDF should be text searchable and should include a contents table featuring hyperlinks to bookmarked pages

Another guidance document to be aware of is the CDISC SDTM Metadata Submission Guidelines.

The guidelines recommend using the following sequence of colors when annotating multiple domains on a single CRF page or collection screen, which can apply in a lot of cases. These colors have been tested to reduce difficulties for individuals with color-blindness.

The Red-Blue-Green (RBG) color codes are also provided above to allow you to apply the colors. If you need to use more than four colors on your CRF pages, the MSG advises you should be consistent and consider accessibility.

BLUE	**YELLOW**	**BLUE**	**ORANGE**
DM	DS	SC	VS
(Demographics)	(Disposition)	(Subject Characteristics)	(Vital Signs)
R 191	R 255	R 150	R 255
G 255	G 255	G 255	G 190
B 255	B 150	B 150	B 155

The challenges of manual annotations

As we've seen, the regulatory guidance is very specific about how annotated CRFs should be prepared, formatted and submitted. This means that preparing CRF annotations manually is not an easy task.

Here's what manual annotated CRF creation typically looks like:

1. Open a PDF form and identify all annotations for each question and section
2. Add each annotation in the correct place, setting the color and font
3. Create bookmarks
4. Review the PDF
5. If there's any changes to make, merge them and update the annotations
6. Redo bookmarks
7. Go through the review process again (steps 4 to 7)
8. And finally, finalize the CRF
9. Now repeat for the rest of the forms in your study!

Now here's why this manual process is such a challenge:

- Each form can have multiple annotations and multiple sources of data. Each annotation will have to be identified and entered manually each time. This makes it very time consuming to do annotations by hand.
- There's an increased risk of human error with manual annotations, because formatting can't be enforced. This means that annotations will have to be peer-reviewed for accuracy, perhaps multiple times, adding more unnecessary delays to the set-up stages of your clinical trial.
- The color and placement of the annotations as detailed in the FDA guidance is very specific. It can be fiddly and monotonous to ensure each one meets the required format.
- After spending all that time manually creating annotations, this effort has to be repeated time and time again for every form in every study.

Automating annotated CRF creation

It's fair to say that doing annotations by hand is a big headache. So, what's the solution?

Using a clinical trial design software, such as Pinnacle 21 Enterprise, allows you to avoid the repetitive and time-consuming manual task by automating the process through standardization.

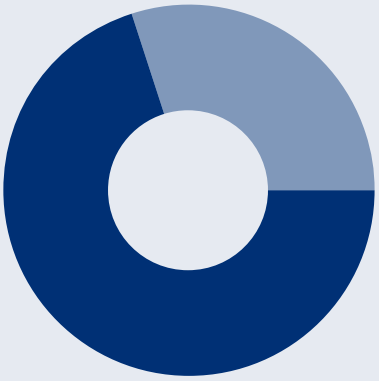
How does it work?

The Features	The Benefits
You can set up a standard format so that the color, position, and text is always consistent.	You don't need to tweak each annotation manually, which means far less fiddly work for you!
The standardized annotations become part of your form standards, which you can reuse in other studies.	This means you've got a standardized aCRF ready as soon as you've built your study.
You can also reuse your standardized metadata across different forms and studies.	So, you won't have to recreate them over and over, saving you time and effort on future studies too.
Bookmarks are updated automatically.	Which means there's no need to redo them each time you make a change.
You can easily edit forms and annotations.	No requirement to manually merge or update changes.
You can instantly preview changes once they have been made.	This makes the CRF review process a lot easier for you and each approver.

What's the difference between data and metadata?

Put simply, 'data' refers to collected responses and 'metadata' describes what's being collected.

In a case report form, the questions contained on the form, the predefined responses to these questions ('Yes', 'No', 'Unknown'), and the annotations are the **metadata.** The answers themselves form the **data.**

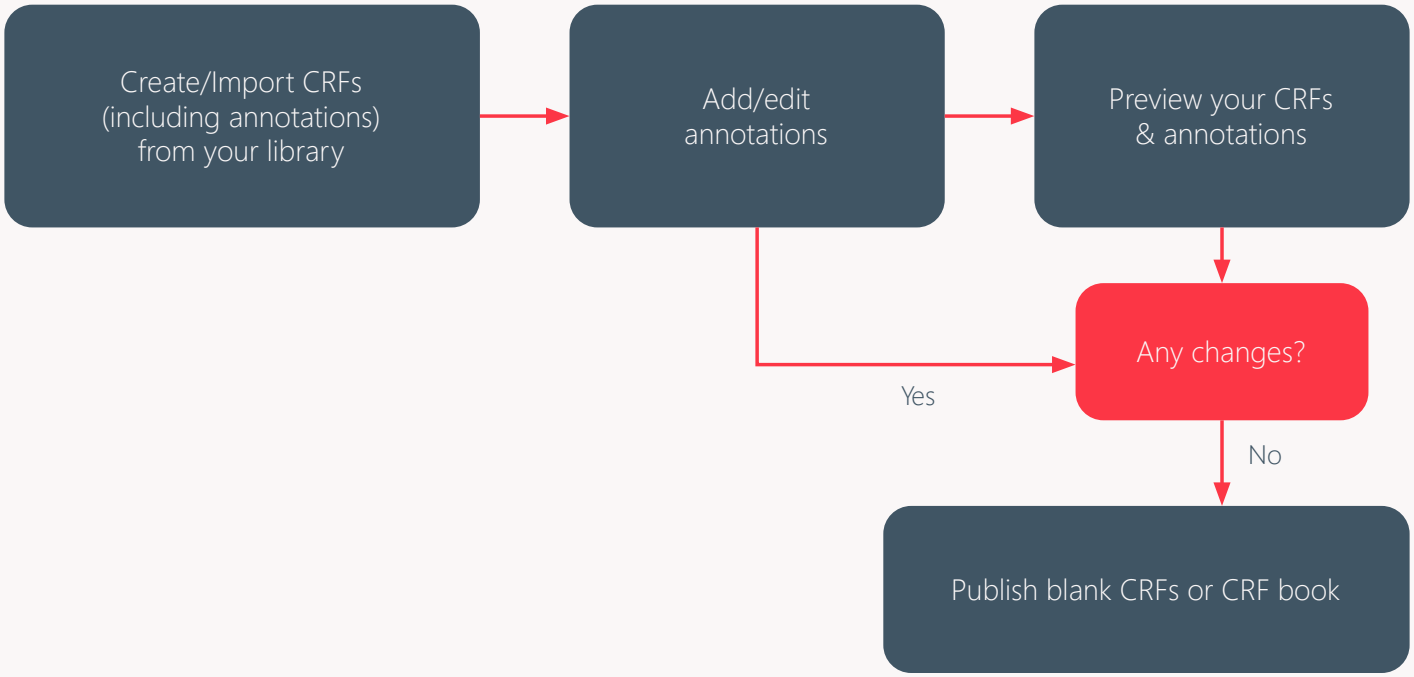


On average, Pinnacle 21 Enterprise helps achieve up to **70% reuse of metadata.**

This improves metadata quality and avoids the need for repetition of time-consuming tasks.

The automated creation process for new and existing content

- Create/Import CRFs (including annotations) from your library
- Add/edit annotations
- Preview your CRFs & annotations
- Any changes?
- Publish blank CRFs or CRF book



CERTARA

What's next?

If you want to find out more about how Pinnacle 21 can help you ditch the manual design process for a streamlined, automated set up, why not have your own customized demo?

There's no commitment and it's totally free.

Book a Demo

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,600 biopharmaceutical companies, academic institutions and regulatory agencies across 70 countries.

Visit certara.com

CERTARA