Paper PP02

Guideline for submission ready aCRF

Christina Paul, Grünenthal GmbH, Aachen, Germany
Stefanie Sturm, HMS Analytical Software GmbH, Heidelberg, Germany

ABSTRACT

In July 2017 a sub team of the German Speaking CDISC User Network was built to develop a Guideline for submission ready aCRF. Several sources have been reviewed (e.g. CDISC, FDA) to collect information HOW to annotate a submission ready CRF (aCRF). The guideline will consolidate the requirements, formats and technical prerequisites, as well as examples on how to put annotations on a submission ready aCRF. The poster will provide information about the planned content of the guideline, the status and the challenges the sub team has to deal with.

INTRODUCTION

For submissions of a trial to a regulatory authority, an annotated CRF would usually be expected to be delivered with the data. There are guidelines in place from different organizations and authorities that provide varying levels of details on how such an annotated CRF should look like, the format of the document and any naming conventions.

Checking all of the different sources before creating an annotated CRF takes quite some time and effort. The "Guideline for a submission ready aCRF" should make it easier to gain on overview of existing recommendations and how to practically implement these when an annotated CRF is set up.

BACKGROUND

The CDISC German User Network is a group of german speaking people who participate in the exchange and discussion about CDISC Standards. It is officially referred to as "CDISC DACH User Network", where DACH stands for Deutschland (Germany), Austria, Confoederatio Helvetica (official Latin name for Switzerland).

Most of the active members are from the pharmaceutical industry and from CROs, but everyone is welcome to join the user network. During monthly conference calls and two face-to-face meetings per year, different CDISC topics are discussed and experiences are exchanged.

During the face-to-face meeting in spring 2017, the idea of a working group that would focus on topics of high interest in the community came to light.

A survey was started in the German User Network to assess the potential topics and to find volunteers for the working group.

In July 2017, the results of the survey were available. The majority of the participants voted for the topic "How to create a submission ready annotated CRF" and the following people agreed to join the working group:

Eva Bervar, Bayer AG
Stefan Bordasch, Abbvie Deutschland GmbH & Co. KG
Christina Paul, Grünenthal GmbH
Torsten Petsching, Boehringer Ingelheim Pharma GmbH & Co. KG.
Petra Rein, PAREXEL International GmbH
Michael Schmitz, Bayer AG
Markus Stoll, Merck KGaA
Stefanie Sturm, HMS Analytical Software GmbH

WHAT HAPPENED UNTIL NOW

After the members for the working group were nominated and the scope of work was defined, an initial meeting took place. A list of potential sources for information regarding the setup of an annotated CRF was developed. The review of these different sources was divided and assigned to the different participants. During the next months, all guidelines, papers, etc. found from the different sources were collected and reviewed for relevancy.

As the working group consists of team members from different pharma companies and CROs, their experiences were also gathered and brought together in an overview of "best practice" approaches.

All relevant information was finally structured by topic and compiled into one document. The chapters were assigned to different working group members for review and revision (e.g. adding of references to source documents, inclusion of examples). Additionally, open questions were collected and discussed in several meetings.

NEXT STEPS

There are still open questions where an agreement needs to be taken in the group. Additionally, further examples should be created and inserted into the document. Afterwards, a review of the complete guideline by all working group members is planned. Once the group has agreed on the guideline, it will be released to the community. The release is currently planned for end of 2018.

IDENTIFIED SOURCES

The following potential sources were identified and have been checked for any information on the setup of an annotated CRF:

- CDISC
- FDA
- PMDA
- EMA
- PhUSE
- TMF – Technologie- und Methodenplattform für die vernetzte medizinische Forschung (according to TMF web page: TMF is the umbrella organization for networked medical research in Germany)
- University Münster, Germany, Institute of Medical Informatics
- CDISC ODM-XML Team (contacted member: Jozef Aerts)

The following documents were identified as main drivers regarding expectations on the annotated CRF:

- CDISC: SDTM Metadata Submission Guideline
- FDA: Study Data Technical Conformance Guide
- FDA: Portable document format specifications

CONTENT OF THE ANNOTATION GUIDELINE

The following structure is planned for the first release of the annotation guideline:

1. Introduction and Purpose
2. Prerequisites / Recommendations
3. Format
4. Bookmarks
5. Table of Content (TOC)
6. Annotations
7. Glossary

This version will focus on recommendations stipulated in the different source documents. It will also include examples and best practice approaches.

The examples displayed on the poster relate to the different chapters of the annotation guideline. They are based on the current draft version of the document, i.e. changes are still possible.

RECOMMENDATION: ANNOTATIONS

The annotation examples show the difficulties in interpreting what is specified in the FDA Study Data Technical Conformance Guide version 4.1, March 2018, chapter 4.1.4.6: "The annotated CRF should provide the variables names and coding for each CRF item included in the data tabulation datasets."

Different scenarios would be possible:
Approach 1:
Follow the guidance provided in the CDISC Study Data Tabulation Model Metadata Submission Guide, version 1.0 Final, 13-Dec-2011, chapter 4.1.3. In this case, only the codelist value for the parameter test code is included in the annotated CRF.

This might not be sufficient as it does not include the "coding" for each CRF item.

For approach 2-4, we need to take a closer look at the phrase "coding for each CRF item". What exactly is meant with "coding"? Should we specify the codelist value? Or should we specify both the codelist name and the codelist value? Or is it enough to only specify the codelist name? For all these cases, the annotation would look slightly different.

This is an open topic that we are still discussing within our working group.

RECOMMENDATION: BOOKMARKS

4. Bookmarks

The annotated CRF is required to contain bookmarks.
Bookmarks should be created in two ways (**dual bookmarking**):

- Chronologically - by time points according to study event schedule with study-level bookmarks (e.g. AE) available last

- Alphabetically - by CRF topics or DCT (sequence used in EDC tool). Available bookmarks within a topic have to be ordered chronologically according to study event schedule, too.

Bookmarks have to reflect forms as many times as needed to give evidence how the data were collected; e.g. "Subject Status" is bookmarked in visits 1, 3, and 5, all three bookmarks would link to the unique subject status page.
Magnification has to be set to "Inherit Zoom".
Bookmarks have to be created at least in chronologically order - this has to be confirmed by reviewer.

Figure 4-1 chronologically bookmarks by visits and alphabetically bookmarks by domains

Two examples how bookmarks can be implemented are displayed. The first example shows the bookmarks set up in a chronological way. The second example shows the bookmarks in an alphabetical structure.
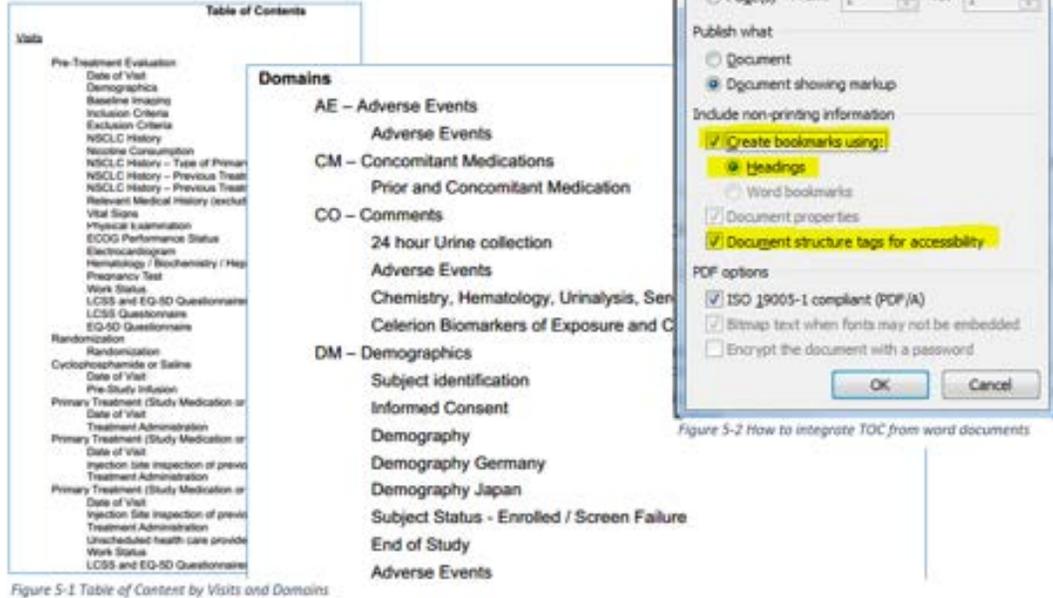
RECOMMENDATION: TABLE OF CONTENT

Figure 5-1 Table of Content by Visits and Domains

Figure 5-2 How to integrate TOC from word documents

The example shows how a Table of Content (TOC) for an annotated CRF might look like. It also provides a short guidance how a TOC can be created.

CONCLUSION

After we had checked the different sources for information on how to set up an annotated CRF, we realized that there are only a few documents where recommendations are available. In these documents, there is a lack of detailed advice regarding the practical implementation of the annotations itself. Therefore we decided to put all the recommendations in one document and add several examples as a sort of "best practices" reference guide.

Once the resulting annotation guideline has been finalized, it will be made available to the community on the wiki pages of the German Speaking CDISC User Network (for link to the web page, see references).

The annotation guideline will be posted in the DACH UN Working Groups/Annotated CRF (aCRF) section.

The guideline should assist in setting up the annotated CRF in an acceptable way for different authorities.

In the long term, it might also be a first step to come to an aligned approach within the industry.

REFERENCES

CDISC
Metadata Submission Guideline:
https://www.cdisc.org/standards/foundational/study-data-tabulation-model-implementation-guide-sdtmig/metadata-submission

FDA
Study Data Technical Conformance Guide:
https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
Portable document format specifications:
https://www.fda.gov/downloads/Drugs/UCM163565.pdf

German Speaking CDISC User Network Wiki
https://wiki.cdisc.org/display/DEUUG/German+User+Network+Home

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors or any working group member at:

Eva Bervar, Bayer AG
eva.bervar@bayer.com

Stefan Bordasch, Abbvie Deutschland GmbH & Co. KG
stefan.bordasch@abbvie.com

Christina Paul, Grünenthal GmbH
christina.paul@grunenthal.com

Torsten Petsching, Boehringer Ingelheim Pharma GmbH & Co. KG.
torsten.petsching@boehringer-ingelheim.com

Petra Rein, PAREXEL International GmbH
Petra.Rein@parexel.com

Michael Schmitz, Bayer AG
michael.schmitz4@bayer.com

Markus Stoll
stolm001@Stoll.onmicrosoft.com

Stefanie Sturm, HMS Analytical Software GmbH
stefanie.sturm@analytical-software.de